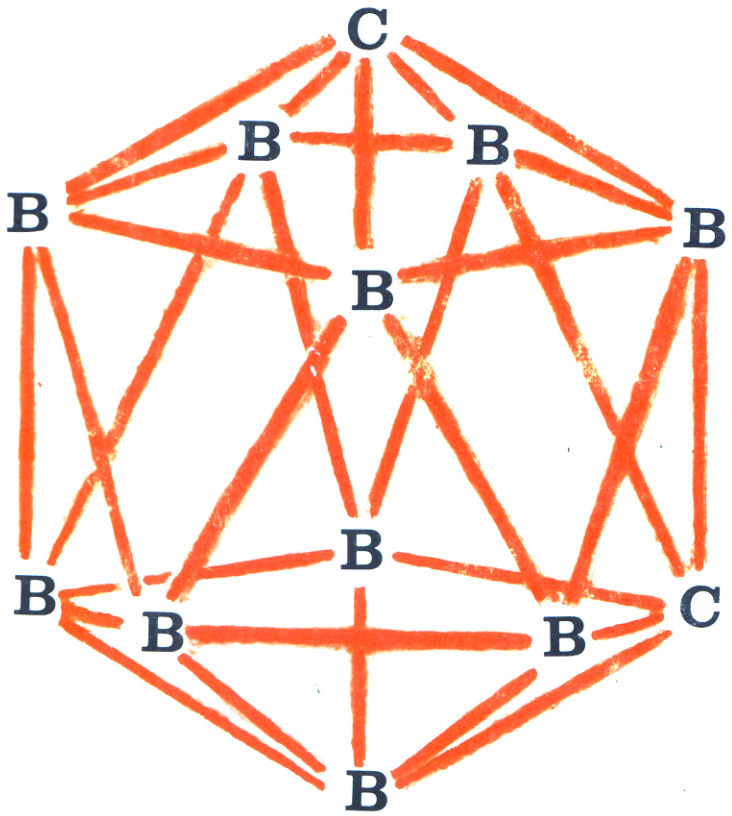
FUNDAMENTALS OF ORGANIC CHEMISTRY

A.N. NESMEYANOV, N.A. NESMEYANOV



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ИЗДАТЕЛЬСТВО МИР

FUNDAMENTALS OF ORGANIC CHEMISTRY

by
A.N. Nesmeyanov
and
N.A. Nesmeyanov

This four-volume textbook is designed for a systematic study of organic chemistry. The material presented in the book is divided into two parts and covers a considerably wider field than does the normal university treatment of the subject. Part One (the first three volumes) is constructed on "classical" lines. Part Two (volume IV) is intended for attentive reading rather than for close study. Volume IV is devoted to the following topics: organoelement compounds; nonbenzenoid aromatic systems; carbanions; free radicals; carbenes; carbonium ions; elimination reactions; isoprenoids; alkaloids of the heterocyclic series; proteins; nucleotides and polynucleotides; enzymes.

This book has been translated from the second revised Russian edition published in two volumes in 1974. The first Russian edition (in two volumes) was published in 1969.

The book may be used for self-study and for reading the course of organic chemistry at universities and chemical higher schools. It will undoubtedly be of interest to post-graduates, teachers, scientists and engineers working in the field of organic chemistry.

FUNDAMENTALS OF ORGANIC CHEMISTRY

Volume IV

А. Н. Несмеянов, Н. А. Несмеянов

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Chapter 12

Organoelement Compounds

The first organometallic compounds had been discovered by the middle of last century. They were investigated in a systematic way by Frankland. These volatile compounds, whose vapour density could be measured and molecular weights determined, were used by Frankland for establishing the concept of valency. A metal in such compounds is linked by a chemical bond to a carbon atom of an organic (aliphatic or aromatic) radical.

There is no sharp boundary line between metals and nonmetals (metalloids). This boundary line is even less pronounced in their organic derivatives, so that the simplest carbon-containing derivatives of the following elements show points of similarity: Bi, Sb, As, and P; Sn, Ge, and Si; Al and B, which can be seen even from the similarity between the forms of compounds of elements of varying degree of alkylation (or arylation). Examples are given in Table 12.1.

TABLE 12.1

Group IV	Group V
$RSiH_3$, R_2SiH_2, R_3SiH, R_4Si $RSiCl_3$, R_2SiCl_2, R_3SiCl	RPH_2, R_2PH, R_3P $RPCl_2$, R_2PCl $RPCl_4$, R_2PCl_3, R_3PCl_2, R_4PCl, R_5P
$RGeH_3$, R_2GeH_2, R_3GeH, R_4Ge $RGeCl_3$, R_2GeCl_2, R_3GeCl	$RAsH_2$, R_2AsH, R_3As $RAsCl_2$, R_2AsCl $RAsCl_4$, R_2AsCl_3, R_3AsCl_2, R_4AsCl, R_5As
$RSnH_3$, R_2SnH_2, R_3SnH, R_4Sn $RSnCl_3$, R_2SnCl_2, R_3SnCl	$RSbH_2$, R_2SbH, R_3Sb $RSbCl_2$, R_2SbCl $RSbCl_4$, R_2SbCl_3, R_3SbCl_2, R_4SbCl, R_5Sb
$RPbH_3$, R_2PbH_2, R_3PbH, R_4Pb $RPbCl_3$, R_2PbCl_2, R_3PbCl	

The area of organometallic compounds was increasingly expanding, being transformed about the middle of this century into **organoelement**, or **elementoorganic, chemistry**, i.e., the chemistry of organic compounds of all the elements. The field of organoelement compounds is basically the field of carbon compounds of the elements, which are unusual for classical organic chemistry, the latter being defined as the chemistry of the elements called organogens (carbon, hydrogen, oxygen, nitrogen, sulphur, chlorine, bromine, iodine, and phosphorus in the form of phosphoric acid esters). Phosphorus thus stands, as it were, at the boundary line between the two areas of organic chemistry. Naturally, each element is present in an organic molecule in the form of one or more functional groups. This will supplement our knowledge of the functional groups—derivatives of the organogenetic elements.

The great majority of the elements of the periodic system are metals. Therefore, more than half of the compounds of organoelement chemistry are **organometallic compounds.** Organometallic compounds are defined as substances in which the carbon atom is directly linked (through a covalent or ionic bond) to the metal involved. But not all metals form stable alkyl compounds. It is mainly non-transition metals that form such compounds (with the exception of Au and Pt).

If an attempt is made to synthesize an alkyl compound of a transition metal, say, cobalt, by means of an exchange reaction:

$$CH_3MgI + CoCl_2 \longrightarrow CH_3CoCl + MgICl$$

then the resulting alkyl derivative of cobalt will decompose even at a temperature below 0°C:

$$CH_3CoCl \longrightarrow CH_3\cdot + CoCl\cdot$$
$$2CH_3\cdot \longrightarrow C_2H_6$$

With a few exceptions, there exist no stable, purely alkyl or purely aryl compounds of transition metals. Transition metals, however, are known to form other types of compounds with a direct carbon-metal bond. These substances are structurally related to inorganic complex compounds. Among them are, for example, the long-known complex cyanides, $K_4Fe(CN)_6$. They also include metal carbonyls, such as $Fe(CO)_5$, $Ni(CO)_4$, $Cr(CO)_3$, etc. Closely related to them are the so-called π-complexes of olefins with transition metals. All these compounds will be discussed at a later time.

12.1. Active Organometallic Compounds of Groups I, II, and III

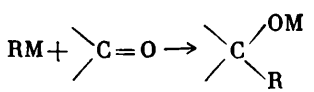
The alkyl and aryl compounds of alkali and alkaline-earth metals, Be, Mg, Zn, Cd, and Al are decomposed by acids, water, and alcohols with the evolution of a hydrocarbon, are oxidized by molecular oxygen. react with carbonyl compounds and enter into a large variety of reactions with other oxygen, sulphur, and nitrogen functional groups, in which the carbon-metal bond is broken. In all these reactions they differ from the alkyl and aryl compounds of Hg, In, Tl, Si, Ge, Sn, Pb, As, Sb, Bi. Organometallic compounds of the alkali metals (except organolithium compounds) are ionic compounds and their reactivity is due to the alkyl (or aryl) anion. Although other active organometallic compounds have a covalent carbon-metal bond, it is so strongly polarized ($\overset{\delta-}{C}—\overset{\delta+}{M}$) that their reactions are generally similar to those of ionic compounds, though they proceed not so vigorously as the latter.

Thus, organic compounds of the alkali metals (except RLi) react with alkyl halides and with aryl halides:

$$RM + R'X \longrightarrow RR' + MX$$

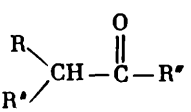
Even organomagnesium compounds react in this way only with allyl halides, benzyls and other types of compounds having a mobile halogen atom (the α-halogen atom of halosubstituted acids, esters, etc.).

Active organometallic compounds react with carbon dioxide by the well-known reaction, forming acids, but organoaluminium and organozinc compounds give this reaction only under more severe conditions. The normal reaction of active organometallic compounds with carbonyl compounds proceed according to the following scheme:

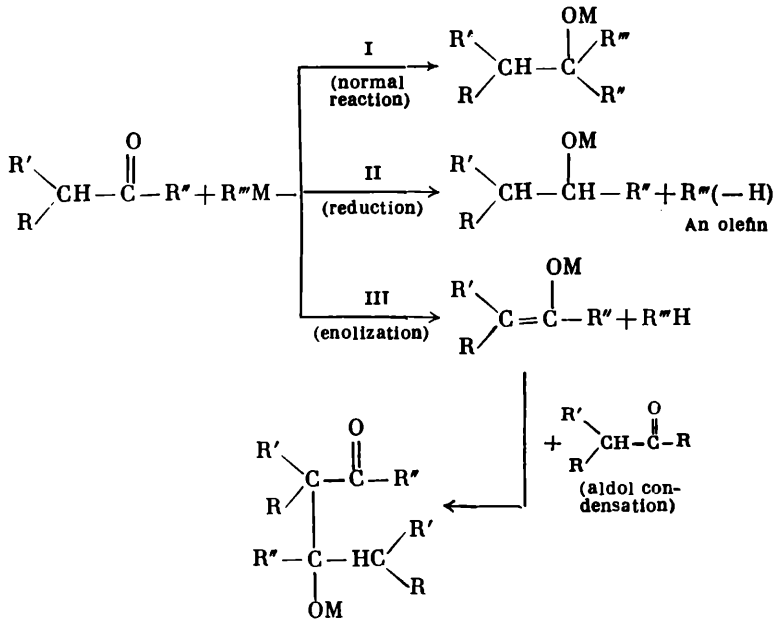


This reaction, however, is accompanied by certain complications (which will be considered in more detail when dealing with organomagnesium compounds), which are especially characteristic of the most active compounds of this kind, i.e., ionic active organometallic compounds or those more closely related to them.

In the case of carbonyl compounds of the general structure

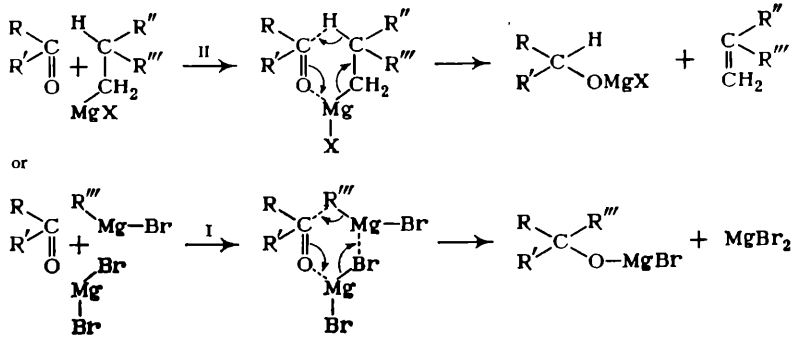


the reaction may proceed in several directions, and whether this or that direction predominates depends on the nature of the radical (its electronegativity), the metal, the radical-metal bond (the degree of ionic character), and on the steric hindrances created by the radicals R, R′, R″, and R‴:



The steric hindrances suppress the normal reaction I and have little effect on reactions II and III. For reaction II (reduction by hydrogen due to R‴) to be accomplished it is necessary that the radical R‴ contain a β-hydrogen capable of migrating in the form of a hydride ion to the carbonyl compound so that the radical R″ could be converted into olefin R‴ (minus H). For reaction III to take place, the carbonyl compound must contain a hydrogen atom. Organosodium and organopotassium compounds predominantly react by path III if only the carbonyl compound involved has an alpha-hydrogen atom. The route taken by the reactions of organolithium and organomagnesium compounds depends on the nature of the radical attached to the metal. The least complicated are the reactions of methyl, benzyl, phenyl, and acetyl derivatives, which take route I; the most complicated are the reactions of compounds with aliphatic and alicyclic secondary radicals, which take route II and, depending on the type of carbonyl compound, by route III. The side reactions (II) as well as the main reaction (I) probably proceed via the six-membered reaction complex (transition state) which may involve an

additional molecule of MgX_2:



12.2. Group I of the Periodic System

Organometallic Compounds of the Alkali Metals. 1. Alkyl and aryl halides react with the alkali metals in inert solvents (hexane, octane, and also benzene for lithium), forming alkyl and aryl derivatives of alkali metals. The situation, however, is complicated even in the case of sodium by the Wurtz reaction which proceeds through stage (1) and further by reaction (2); for potassium the reaction can seldom be stopped at stage (1):

$$RCl + 2M \longrightarrow RM + MCl \quad (1)$$

$$RM + RCl \longrightarrow R{-}R + MCl \quad (2)$$

The compounds RNa thus obtained can be used for many (but not for all) types of reactions similar to reactions of Grignard reagents (P. P. Shorygin, Morton). Since organolithium compounds are more convenient to handle and are also more soluble than all the organic compounds of the other alkali metals, they find wide application in synthetic work, especially in syntheses involving Grignard reagents. Besides, the synthesis of organolithium compounds presents less difficulties in choosing the solvent: they can be prepared both in paraffin hydrocarbons and in benzene, and in many cases (methyllithium, phenyllithium) even more preferably in ether.

Alkylsodium and arylsodium compounds and the corresponding compounds of potassium are solid colourless ionic substances which are insoluble in solvents. Benzylsodium and triphenylmethylsodium are soluble in ether, have a cherry-red colour (the colour of the anion), and their solutions are conductors of electricity. Methyllithium, ethyllithium, and aryllithium are solid compounds, but other lithium alkyls are liquids. They are all soluble in inert solvents. Benzyllithium and triphenylmethyllithium are similar to the corresponding

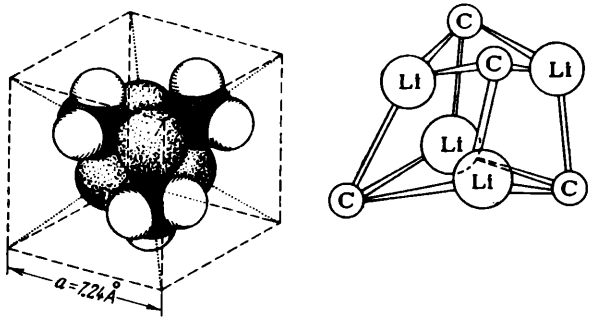


Fig. 12.1.
The models of the methyl-lithium tetramer (hydrogen atoms not shown).

compounds of sodium. The compounds of potassium, rubidium and cesium have been studied much less thoroughly. Lithium alkyls are in the associated state in solutions (the degree of their polymerization varies from 2 to 6), and methyllithium is a tetramer (Fig. 12.1) in which not electron pairs but multicentre orbitals are involved in the formation of bonds. The carbon atoms in $(CH_3Li)_4$ have a coordination number of 5. Bridging methyl groups of this kind will be dealt with in discussing organoaluminium compounds, and bridging hydrogens—in the treatment of boron hydrides. All alkyl and aryl compounds of the alkali metals are spontaneously inflammable in air, are decomposed vigorously under the influence of alcohols, water and acids.

Apart from the above-described synthesis from halogen derivatives and a metal, the simplest organic compounds of the alkali metals can be obtained by the following methods.

2. The action of a metal on organomercury compounds:

$$R_2Hg + 2M \longrightarrow 2RM + Hg$$

3. The reaction of lithium alkyls with aryl or alkyl halides:

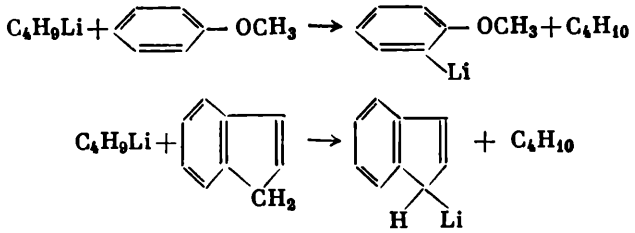
$$RX + R'Li \longrightarrow RLi + R'X$$

4. The direct **metalation** (i.e., the replacement of hydrogen by a metal) involving the action of alkyl derivatives of the alkali metals on aromatic hydrocarbons (the Shorygin reaction which has been thoroughly worked out for lithium by Gilman) and, in general, on substances with a mobile hydrogen atom. For example,

$$CH_3Na + C_6H_6 \longrightarrow C_6H_5Na + CH_4$$

$$CH_3Na + C_6H_5CH_3 \longrightarrow C_6H_5CH_2Na + CH_4$$

$$C_6H_5Na + C_6H_5CH_3 \longrightarrow C_6H_5CH_2Na + C_6H_6$$



The metalation reaction proceeds in such a way that the metal occupies the place of the more replaceable hydrogen. Thus, this reaction makes it possible to construct an acidity scale for hydrocarbons; the acidity of hydrocarbons cannot be measured by ordinary physico-chemical methods. For instance, from the Shorygin reaction it can be clearly seen that the hydrogens of the methyl group of toluene are more acidic than those of benzene.

In the case of the most "acidic" hydrocarbons, such as acetylene, cyclopentadiene, indene, and fluorene, reactions of this type proceed especially easily:

$$HC\equiv CH + 2C_6H_5Na \longrightarrow NaC\equiv CNa + 2C_6H_6$$

The metalation of these hydrocarbons can be carried out even without the use of an organometallic compound, simply by the action of a solution of an alkali metal in liquid ammonia or of sodamide

$$HC\equiv CH + 2NaNH_2 \longrightarrow NaC\equiv CNa + NH_3 + H_2$$

$$HC\equiv CH + NaNH_2 \longrightarrow NaC\equiv CH + NH_3$$

or of potassium hydroxide (if water is distilled off) in the case of fluorene and indene.

5. Organolithium and organosodium compounds enter into the following exchange reaction with aryl bromides and aromatic bromosubstituted heterocycles:

$$ArBr + RM \longrightarrow ArM + RBr$$

This reaction is frequently employed for the synthesis of lithium- and sodium-containing aromatic and heterocyclic derivatives with Li (or Na) in a definite position.

6. P. P. Shorygin has found that on heating sodium is capable of splitting aromatic ethers according to the following equation:

$$C_6H_5OC_6H_5 + 2Na \longrightarrow C_6H_5Na + C_6H_5ONa$$

Particularly readily broken is the linkage in benzyl ethers. Such a cleavage was extensively used by Ziegler for synthesizing organo-

potassium compounds of the benzyl type:

$$C_6H_5C(CH_3)_2-OC_6H_5+2K \longrightarrow C_6H_5\bar{C}(CH_3)_2\ K^+ + C_6H_5OK$$

Finally, there are two further important routes to the formation of organometallic compounds of the alkali metals, which have a specific structure.

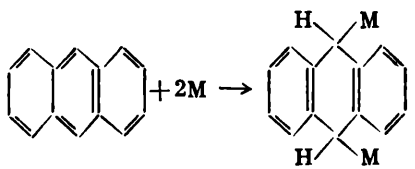
7. The addition of a metal to hydrocarbons having a system of conjugated π-bonds, including aromatic compounds. This addition reaction is believed to begin invariably in the following manner: a hydrocarbon accepts an electron from an alkali metal (which occupies the lower of the empty orbitals) and an ionic pair, $[C_nH_{2n-6}]^-M^+$, is formed. In this way benzene adds only potassium:

$$C_6H_6+K \longrightarrow [C_6H_6]^-\ K^+$$

Naphthalene gives an adduct even with sodium:

This may be followed by a further addition of the metal.

Anthracene forms an adduct both with sodium and lithium, adding two metal atoms:



Such insoluble coloured compounds afford, on hydrolysis, dihydroaromatic hydrocarbons.

The fundamental investigations into the addition of alkali metals to unsaturated and aromatic compounds have been conducted by Schlenk.

The following are two examples illustrating the behaviour of olefinic linkages conjugated with aromatic nuclei under the action of alkali metals:

$$C_6H_5CH=CHC_6H_5+2Na \longrightarrow C_6H_5-\underset{\displaystyle Na}{\underset{|}{CH}}-\underset{\displaystyle Na}{\underset{|}{CH}}-C_6H_5$$

$$2(C_6H_5)_2C=CH_2+2Na \longrightarrow (C_6H_5)_2\underset{\displaystyle Na}{\underset{|}{C}}-CH_2CH_2-\underset{\displaystyle Na}{\underset{|}{C}}(C_6H_5)_2$$

These examples illustrate the fact that open-chain π,π-conjugated systems add a metal to those carbon atoms of the conjugated system which bear aromatic substituents. If only one carbon atom in an unsaturated open chain carries aromatic substituents, the metal atom adds on to it and the molecule is dimerized.

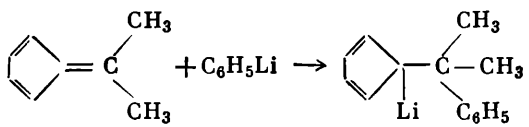
What is meant here is basically the transfer of electrons by sodium atoms to carbon atoms and, precisely, to those which delocalize the captured electrons more readily, say, over aromatic nuclei or along the conjugated system of π-bonds. Simple olefins do not add sodium. In the above and following formulas of the products of addition of alkali metals to unsaturated hydrocarbons the alkali metal-carbon bond might be represented more correctly in an electrovalent (i.e., ionic) form; for example:

$$C_6H_5-\overline{C}H-\overline{C}H-C_6H_5$$
$$Na^+ \quad Na^+$$

Purely aliphatic 1,3-diene systems polymerize under the action of alkali metals (this process forms the basis, say, of the synthesis of sodium-butadiene rubber).

8. The addition of organometallic compounds of alkali metals across conjugated double bonds. The alkyl (often, also aryl) compounds of alkali metals add to olefinic double bonds conjugated with an aromatic ring (1), to fulvenes (2) and dienes (3):

$$(C_6H_5)_2C=CH_2+C_4H_9Li \longrightarrow (C_6H_5)_2\underset{\displaystyle Li}{\underset{|}{C}}-CH_2C_4H_9 \qquad (1)$$



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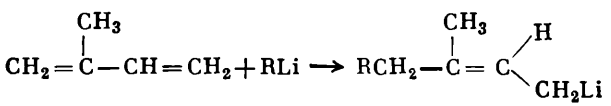
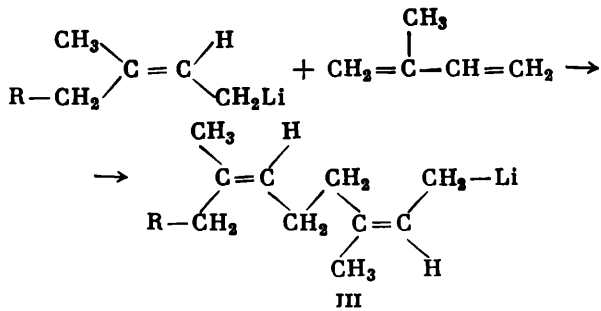


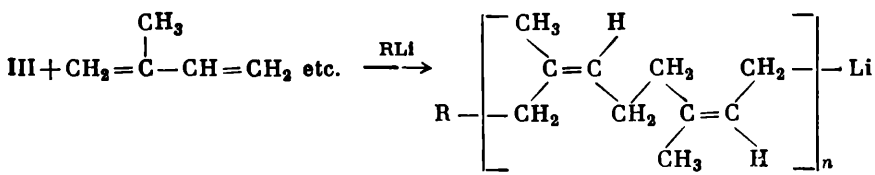
(3)

I II

In the last case, the organometallic product of the primary addition is capable of further adding on to the next molecule of the diene, etc., so that polymerization takes place. When organolithium compounds are used for polymerization of isoprene, for example, the process occurs stereospecifically, and *cis*-polyisoprene is formed, which

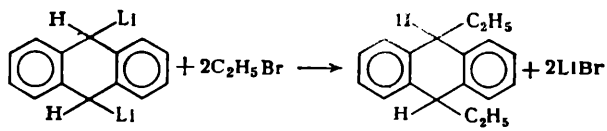
is identical with natural rubber (see Volume I, page 379):





Sodium-isoprene rubber is not stereoregular. Moreover, both this rubber and sodium-butadiene rubber are formed by 1,4-addition as well as by 1,2-addition, so that not only the stereochemistry but also the structure of sodium rubbers has an irregular character.

9. A distinctive feature of organolithium and organosodium compounds is the ability to be alkylated by alkyl halides. Even the unstable adducts of two lithium and sodium atoms to aromatic hydrocarbons enter into this reaction, giving rise to dialkyldihydroaromatic hydrocarbons:



A Grignard reagent interacts satisfactorily in this manner only with benzyl halides and halides of the allyl type, often with an allyl migration of a double bond in the latter case (Prévost). In other respects, the reactions of organolithium compounds and their areas of application in syntheses very closely resemble the reactions of organomagnesium compounds that will be described at a later time. The same can be said about organosodium compounds as far as the type of reactions is concerned, omitting specific details. Organosodium compounds, however, have a number of disadvantages. They are insoluble in inert solvents (form ion pairs), react more vigorously than organolithium and organomagnesium compounds, and often when they are used such reactions as enolization or the condensation

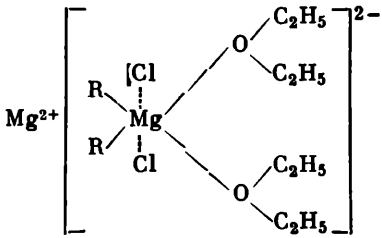
of the resulting enolates (page 29) take place especially rapidly, i.e., side reactions predominate rather than the reactions leading to the desired products. This refers, even to a greater extent, to organopotassium compounds.

12.3. Group II of the Periodic System

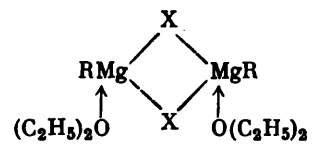
Organomagnesium Compounds. Two types of organomagnesium compounds are known: R_2Mg and RMgX (where X = halogen). Organomagnesium compounds of the general formula R_2Mg can be prepared via organomercury compounds (by the action of metallic magnesium) or from compounds of the type RMgX. Organomagnesium halides, RMgX, which are called **Grignard reagents***, are obtained most frequently by the action of alkyl halides and other halogen-substituted hydrocarbons on metallic magnesium in a solution of diethyl ether, which significantly speeds up the reaction:

$$RX + Mg \xrightarrow{f} RMgX$$

In fact, the complexed ether enters into the composition of an organomagnesium compound. Besides, according to the ebullioscopic determinations made by A. P. Terentiev, a Grignard reagent has a doubled molecular weight. When its ethereal solution is subjected to electrolysis, magnesium is deposited on the cathode. All this led Terentiev to suggest the following structure for the Grignard reagent:



Ashby and Walker (1967) put forth arguments in the favour of the association of the Grignard reagent being accomplished by halogen bridges (in just the same way as, for example, in ferric chloride, Fe_2Cl_6):



* After Victor Grignard (1871-1935) who was awarded the Nobel Prize in 1912 for his researches in this field.— *Tr.*

Such a structure, however, does not account for the fact of the electrical conduction and electrolysis of ethereal solutions of the Grignard reagent with transfer of Mg^{2+} to the cathode if the equilibrium established by Schlenk is not taken into account. Schlenk has found that R_2Mg, $RMgX$, and MgX_2 linked to ether are in equilibrium in the Grignard reagent. By adding dioxan (see Volume I, page 161) it is possible to deposit the last two compounds, with only R_2Mg being left in solution (the equilibrium is set up rather slowly). In spite of the more complex structure of Grignard reagents, all their reactions can be quite satisfactorily described with the aid of the formula RMgX, which is the one usually employed at present. But, in general, the discussion of the plausible structure for the Grignard reagent cannot be considered to be completed.

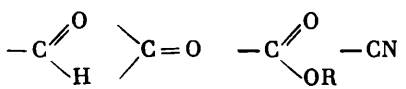
Tetrahydrofuran has recently been proposed as a more suitable medium than ethyl ether for carrying out Grignard reactions. In tetrahydrofuran, organometallic compounds are readily formed from those halogen derivatives which do not react in ether. For example, $CH_2=CHMgBr$ is formed from $CH_2=CHBr$ in tetrahydrofuran (Normant).

The most vigorous reaction with magnesium is afforded by alkyl iodides, but the best yields are provided in the case of alkyl bromides and especially by reactions with alkyl chlorides. Aromatic Grignard reagents are usually prepared from aryl iodides or aryl bromides since aryl chlorides enter into reaction only at temperatures above 100°C.

Allyl halides, beginning with $CH_2=CH-CH_2Cl$, when allowed to react with magnesium very readily give diallyl as the result of the Wurtz reaction. Nevertheless, they can be brought into reaction with a Grignard reaction even in ether if an ethereal solution of an allyl halide is added gradually, drop by drop, to magnesium in the cold. From dihaloalkanes there are formed dimagnesium halides only from halogen derivatives in which there are, at least, four carbon atoms between the halogens:

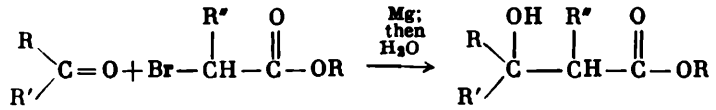
$$ClCH_2CH_2CH_2CH_2Cl + 2Mg \longrightarrow ClMgCH_2CH_2CH_2CH_2MgCl$$

In the aromatic series, *m*- and *p*-dibromobenzenes form $C_6H_4(MgBr)_2$; the same reaction is shown by 1,4-dibromonaphthalene. It is natural that the halogen derivatives of the aliphatic, alicyclic, and aromatic series, which form Grignard reagents, must have no substituents capable of interacting with the reagent; examples of such substituents are:



The molecule of a halogen derivative may contain ether and tertiary amino groups, but not at the carbon atom to which the halogen

is directly attached and not at the carbon atom next to it. The only exception is the esters of α-halogenocarboxylic acids, which react with magnesium in the presence, say, of carbonyl compounds by the Reformatsky reaction (cf. page 35):



Mention should also be made of perfluoroalkyl Grignard reagents which have found wide application. Iodides of the general structure $C_nF_{2n+1}I$ react with magnesium in the cold in ether, and even better in tetrahydrofuran, forming $C_nF_{2n+1}MgI$. This reaction is most difficult to carry out in the case of CF_3I (—72°C, tetrahydropyran). The products that are readily obtained are $CF_2{=}CFMgI$ and C_6F_5MgI.

The method of exchange of a halogen for a metal under the action of an organometallic compound, which is important for the synthesis of organolithium compounds, is of no value in a Grignard reaction. A very important method is the replacement of an active hydrogen by MgX under the action of a Grignard reagent. The following reactions which we have already encountered in the text illustrate the preparation of valuable organomagnesium compounds by this "indirect" way:

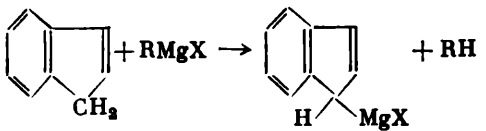
$$HC{\equiv}CH + 2RMgX \longrightarrow XMgC{\equiv}CMgX + 2RH$$

Iotsich reagent

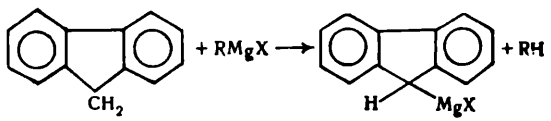
$$HC{\equiv}CH + RMgX \longrightarrow HC{\equiv}CMgX + RH$$

(excess, under pressure)

Cyclopentadiene



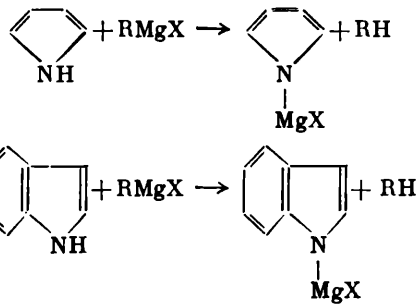
Indene



Fluorene

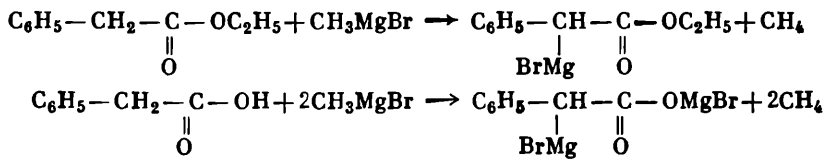
All organomagnesium compounds obtained by the replacement of mobile hydrogen at carbon are somewhat less active than ordinary aliphatic and aromatic Grignard reagents.

No less important are the organomagnesium derivatives of pyrrole, indole, and other nitrogen-containing five-membered heterocycles having a N—MgX bond:



They usually react with transfer of the reaction centre via the α-carbon atom (pyrrylmagnesium halide, see Volume III, page 431) or via the β-carbon atom (indenylmagnesium halide, Volume III, page 282).

The α-hydrogen atom in phenylacetic ester or phenylacetic acid and its salts is also mobile. By reacting these compounds with a Grignard reagent the Bulgarian scientist Ivanov prepared and extensively used special organomagnesium compounds in synthetic work:



Grignard Reactions. 1. Compounds with an active hydrogen, those of the type H—A, i.e., all acids, water, alcohols, and other hydroxy derivatives, ammonia, primary and secondary amines, amides, mercaptans, etc., react with a Grignard reagent according to the following scheme:

$$RMgCl + H-A \longrightarrow R-H + A-MgCl$$
$$RMgCl + HOH \longrightarrow RH + HOMgCl$$
$$RMgCl + HOCH_3 \longrightarrow RH + CH_3OMgCl$$
$$RMgCl + RNH_2 \longrightarrow RH + RNHMgCl$$
$$RMgCl + R'SH \longrightarrow RH + R'SMgCl$$

The reaction forms the basis of the method used for determination of an active hydrogen atom from the amount of methane evolved from CH_3MgI (the Tserevitinov-Chugaev method significantly improved by A. P. Terentiev).

2. The halogens, oxygen, and sulphur cleave the C—Mg bond in the Grignard reagent:

$$RMgX + X_2 \longrightarrow RX + MgX_2$$

$$RMgX + \tfrac{1}{2}O_2 \longrightarrow ROMgX \xrightarrow{H_2O} ROH + Mg\begin{matrix}OH\\X\end{matrix}$$

$$RMgX + S \longrightarrow RSMgX \xrightarrow{HX} RSH + MgX_2$$

3. Carbonyl compounds add a Grignard reagent (see Volume I, page 128):

$$RMgCl + CH_2O \longrightarrow RCH_2OMgCl \xrightarrow{H_2O} RCH_2OH + Mg\begin{matrix}OH\\Cl\end{matrix}$$

$$RMgCl + R'-C\begin{matrix}=O\\H\end{matrix} \longrightarrow \begin{matrix}R\\R'\end{matrix}CHOMgCl \xrightarrow{H_2O} \begin{matrix}R\\R'\end{matrix}CHOH + Mg\begin{matrix}OH\\Cl\end{matrix}$$

$$RMgCl + \begin{matrix}R'\\R''\end{matrix}C=O \longrightarrow \begin{matrix}R\\R'\end{matrix}-COMgCl \xrightarrow{H_2O} \begin{matrix}R\\R'\end{matrix}-COH + Mg\begin{matrix}OH\\Cl\end{matrix}$$

Grignard himself assigned the formulas given here to the adducts of carbonyl compounds, but later (Hess, 1921) it was found that these adducts have the structure of molecular compounds of the type

$$\begin{matrix}R'\\R''\end{matrix}CO\cdots Mg\begin{matrix}X\\R\end{matrix}$$

A. N. Nesmeyanov and V. A. Sazonova have proved the correctness of Grignard's viewpoint by establishing the identity of the substances obtained by three different routes:

$$\begin{matrix}R'\\R''\end{matrix}C=O + RMgX\cdot O\begin{matrix}C_2H_5\\C_2H_5\end{matrix} \xrightarrow{I} \begin{matrix}R\\R''\end{matrix}-COMgX\cdot O\begin{matrix}C_2H_5\\C_2H_5\end{matrix} \xleftarrow{II}$$

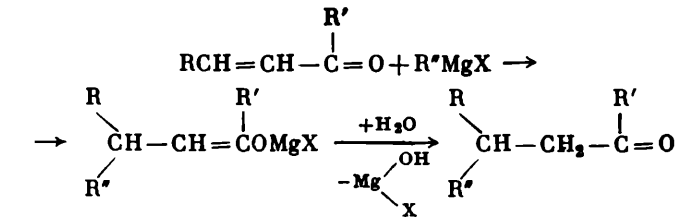
$$\xleftarrow{} \begin{matrix}R\\R'\end{matrix}C=O + R''MgX\cdot O\begin{matrix}C_2H_5\\C_2H_5\end{matrix} \qquad R'-\overset{\uparrow III}{\underset{R''}{\overset{R}{C}}}-OH + CH_3MgX\cdot O\begin{matrix}C_2H_5\\C_2H_5\end{matrix}$$

Like a Grignard reagent, the resulting alkoxide contains ether complexed with magnesium.

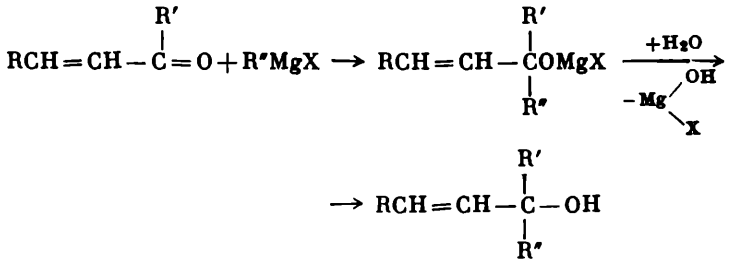
4. Unsaturated ketones with a conjugated system of π-bonds

$$C=C-C=O$$

add a Grignard reagent in the 1,4-positions, which after hydrolysis leads to the formation of a saturated ketone:

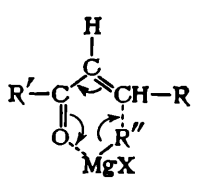


Usually, this reaction takes place concurrently with 1,2-addition which gives an unsaturated tertiary alcohol:



As established by Kohler, the larger the radical R″ the more capable it is of 1,4-addition. The same applies to the radical R′. The compound most capable of normal 1,2-addition is CH_3MgX. The bulkiness of the radical R has an opposite effect. From what has been said it is clear that aldehydes (R′=H) are more capable of 1,2-addition reactions than ketones.

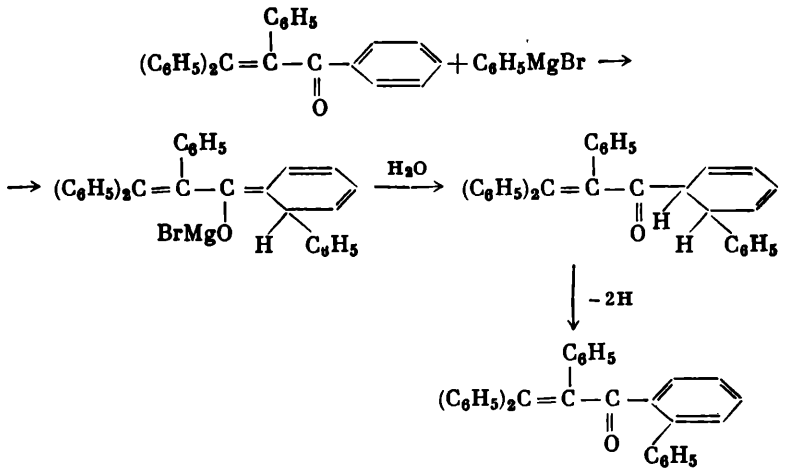
It is believed (Lutz and Reveley) that 1,4-addition proceeds via the six-centre transition state:



The enolate structure of the 1,4-addition product has been proved by Kohler through ozonolysis.

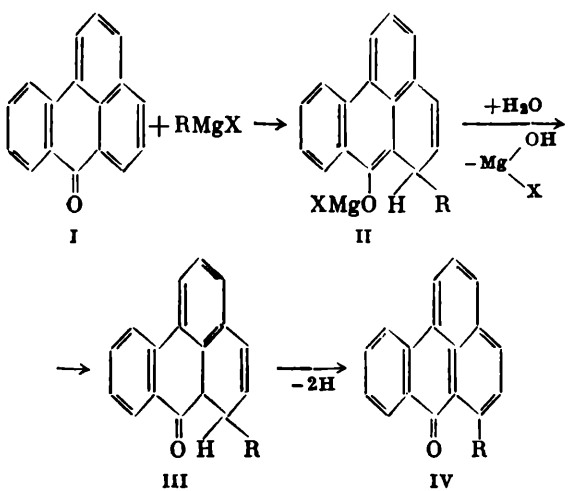
Highly interesting and surprising are the 1,4-additions of Grignard reagents to aromatic ketones with a conjugated system of bonds, C=C—C=O, discovered by Kohler and investigated also by Koelsch and Fuson. In such reactions the radical R of the Grignard

reagent becomes incorporated into the aromatic ring:



It is obvious that this direction of the reaction is caused by steric hindrances to addition across the carbonyl double bond and by the accessibility of the π-system of the benzene ring conjugated with a carbonyl group.

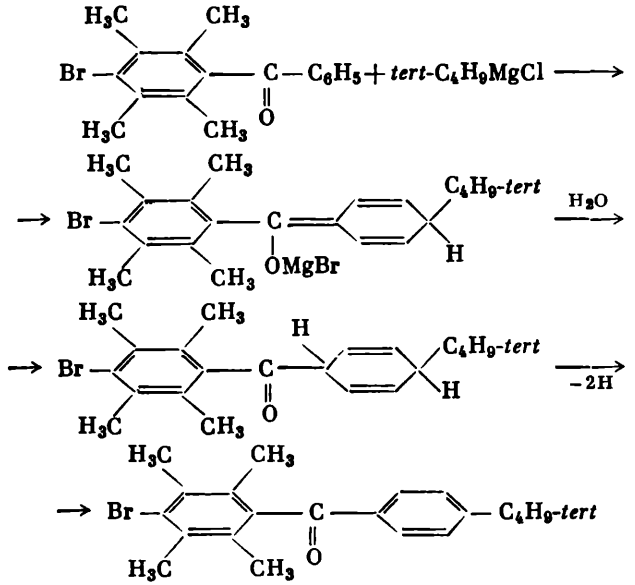
Benzanthrone I reacts with a Grignard reagent also in the 1,4-positions:



The product III formed transiently in this reaction could not be isolated. Losing hydrogen, it apparently is aromatized to product IV.

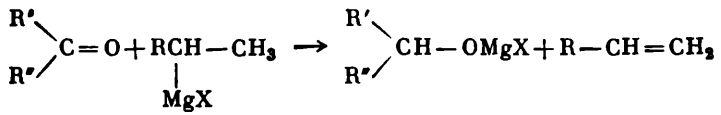
In the case of aromatic ketones sterically hindered to such an extent that the *ortho*-position of the benzene ring is inaccessible the

radical of the Grignard reagent enters the *para*-position, i.e., the 1,6-addition of RMgX takes place (Fuson):

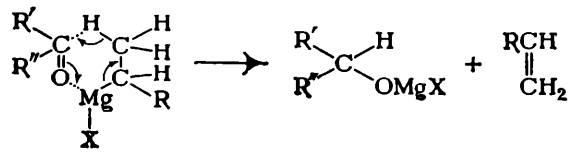


When Grignard reagents interact with carbonyl compounds, particularly when the radical of the Grignard reagent is secondary or tertiary, anomalous reactions occur, which sometimes predominate over the normal reaction. Reactions (a-d) are **abnormal reactions.**

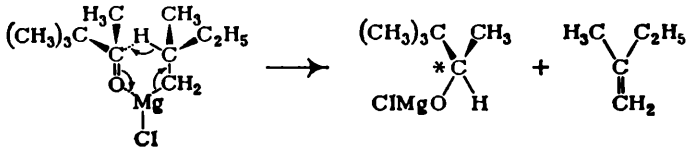
(a) Reduction leading, after hydrolysis, to the formation of a primary alcohol from an aldehyde and a secondary (not tertiary) alcohol from a ketone:



This anomaly has been examined by many scientists. The most plausible explanation has been given by Mosher and La Combe. It boils down to the following: the reaction proceeds through a six-centre transition state with hydride shift (i.e., transfer of hydrogen with an electron pair of a covalent bond) from the β-position of the Grignard reagent to the carbonyl carbon atom:



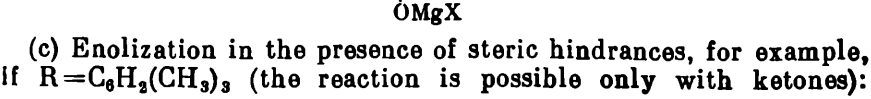
An argument in favour of this scheme is the action of the optically active Grignard reagent D-2-methylbutylmagnesium on pinacoline:



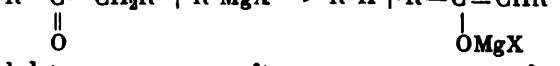
In the cyclic transition state, the two-sided attack by the terminals H and MgX of the Grignard reagent molecule on the flat ketone molecule occurs in such a way that the more bulky substituents —the tertiary butyl and ethyl —are not close to each other on one side of the ring. Therefore, the hydride shift (transfer of H:) leads to the transmission (partial) of optical activity from the Grignard reagent to the secondary alcohol formed.

This reaction, after hydrolysis, gives dextrorotatory pinacoline alcohol.

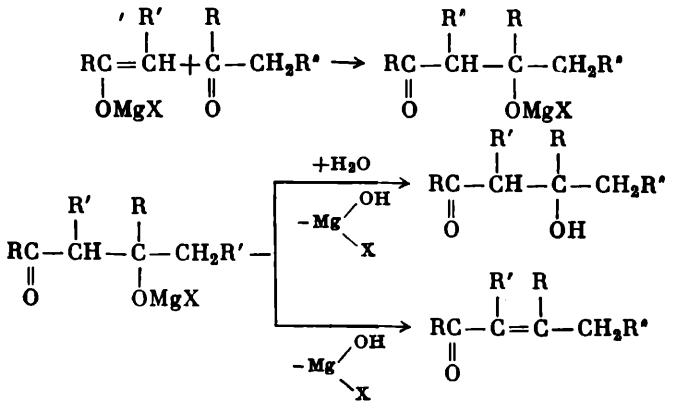
(b) The dehydration of a tertiary alcohol obtained from a ketone, with the formation of an unsaturated hydrocarbon, more exactly, the elimination of MgOHX from the alkoxide of a tertiary alcohol:



(c) Enolization in the presence of steric hindrances, for example, if $R = C_6H_2(CH_3)_3$ (the reaction is possible only with ketones):

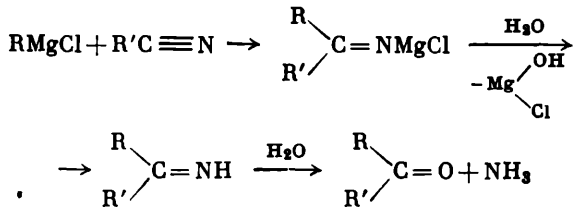


(d) An aldol-type or, more often, croton-type condensation associated with enolization:



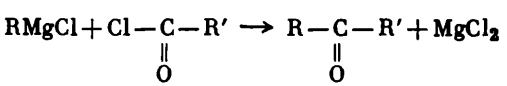
Now we return to normal syntheses with the aid of Grignard reagents.

5. A reaction with a Grignard reagent analogous to that of ketones is shown by nitriles:



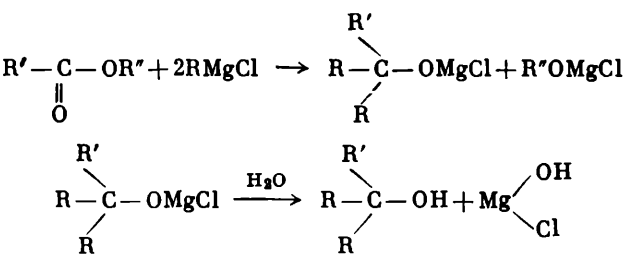
This is the most important method of synthesis of ketones (see Volume I, page 173).

6. The interaction of a Grignard reagent with acid chlorides on cooling also gives ketones:

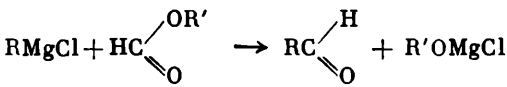


With excess of RMgCl under somewhat more vigorous conditions a tertiary alcohol is formed.

7. Esters react with a Grignard reagent to yield tertiary alcohols:

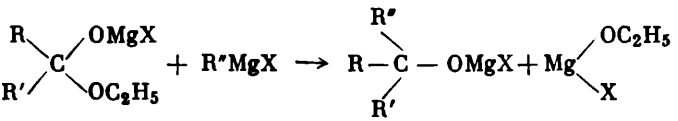


This reaction can seldom be stopped at the stage of formation of ketones. A reaction of this kind is of value only for esters of formic acid. On deep cooling they form aldehydes with a Grignard reagent:

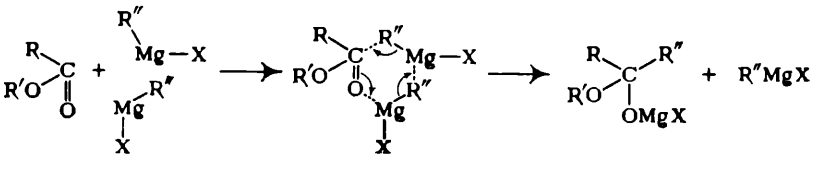


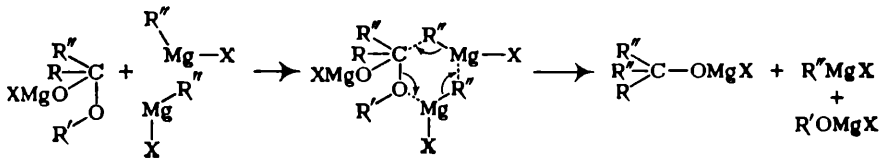
Reactions 5, 6, and 7 begin with addition of a Grignard reagent across a multiple bond, C=O or C≡N (just as with aldehydes or ketones). In the case of esters the second stage of the reaction is the exchange of the alkoxyl residue for the radical of the Grignard re-

agent:



It is possible that the reaction at both stages proceeds with the participation of 2R″MgX via a six-centre transition state (the same mechanism can also be assumed for reactions of organomagnesium compounds with ketones):





A direct exchange of the alkoxyl group occurs in the following examples:

$$RMgX + (R'O)_4C \longrightarrow RC(OR')_3 + R'OMgX$$

Ortho-carbonic ester → Orthoester of acid RCOOH

$$RMgX + RC(OR')_3 \longrightarrow R_2C(OR')_2 + R'OMgX$$

Ketal of ketone R_2CO

$$RMgX + HC(OR')_3 \longrightarrow R-CH(OR')_2 + R'OMgX$$

Acetal of aldehyde RCH=O

The last reaction is the principal method of synthesis of aldehydes with the aid of organomagnesium compounds (A. E. Chichibabin); the acetal is easily hydrolysed in acid medium to yield an aldehyde.

8. With ethylene oxide a Grignard reagent forms a primary alcohol (the chain is built up by two units):

$$RMgX + H_2C\text{—}CH_2 \longrightarrow RCH_2\text{—}CH_2OMgX \longrightarrow RCH_2\text{—}CH_2OH$$

In the case of oxides of the type $R-CH-CH_2$ (with O) there are formed secondary alcohols:

$$R'-HC(O)CH_2 + RMgX \longrightarrow R'-CH(OMgX)-CH_2R \xrightarrow{H_2O} R'-CH(OH)-CH_2R$$

9. An exceptionally important reaction is the reaction of organomagnesium compounds with gaseous or solid carbon dioxide, which leads to the synthesis of acids:

$$RMgCl + CO_2 \longrightarrow R-C(=O)-OMgCl \xrightarrow{HCl} R-C(=O)-OH + MgCl_2$$

10. With nitrogen oxide Grignard reagents react according to the scheme:

$$RMgX + 2NO \longrightarrow R-N(NO)(OMgX) \xrightarrow{H_2O} R-N(NO)(OH)$$

After hydrolysis there are formed alkyl- or arylnitrosohydroxylamine.

11. Nitrosyl chloride interact with a Grignard reagent to give nitroso compounds:

$$RMgCl + ClNO \longrightarrow R-NO + MgCl_2$$

12. The reaction with chloramine (Coleman) and, better, with the O-ester of hydroxylamine (K. A. Kocheshkov and N. I. Sheverdina) gives primary amines:

$$RMgCl + ClNH_2 \longrightarrow RNH_2 + MgCl_2$$
$$RMgCl + NH_2-OCH_2C_6H_5 \longrightarrow RNH_2 + C_6H_5CH_2OMgCl$$

The reactions given are simplified. In fact, excess of the Grignard reagent is taken for the reaction since the replacement of the mobile hydrogen of the amino group by MgX takes place first.

13. From Schiff's bases and a Grignard reagent there are obtained secondary amines (Bush):

$$ArN=CHAr' + RMgCl \longrightarrow Ar'N(MgCl)-CH(Ar')(R) \xrightarrow{H_2O} ArNH-CH(Ar')(R)$$

14. Alkyl- or arylazides react with a Grignard reagent to yield triazenes (i.e., diazoamino compounds):

$$R-N=\overset{+}{N}=\overset{-}{N} + R'MgX \longrightarrow R-N=N-N(R')(MgX) \xrightarrow{H_2O} R-N=N-NH-R'$$

15. Nitroso compounds are converted into N-dialkyl (diaryl hydroxylamines:

$$R-N=O+R'MgX \longrightarrow \begin{matrix} R \\ \diagdown \\ \quad N-OMgX \\ \diagup \\ R' \end{matrix} \xrightarrow{H_2O} \begin{matrix} R \\ \diagdown \\ \quad N-OH \\ \diagup \\ R' \end{matrix}$$

16. The exchange reaction between a salt of a metal with a Grignard reagent affords organometallic compounds (Pfeiffer):

$$4RMgCl+SnCl_4 \longrightarrow R_4Sn+4MgCl_2$$

or

$$2RMgCl+SnCl_4 \longrightarrow R_2SnCl_2+2MgCl_2$$

Most simply obtained in this way are the ordinary or mixed organometallic compounds of all non-transition metals (and the organic derivatives of their metalloid analogues), except the organometallic compounds of the alkali and alkaline-earth metals. In this way, from alkyl and aryl compounds of transition metals there can be obtained and isolated the derivatives of Pt(IV), Au(III), unstable compounds of Cu(I), Ag and some derivatives of titanium.

Kharasch has shown that addition of small amounts of a salt of a transition metal, say, Co(II) (and also $NiCl_2$, $CuCl_2$, etc.) changes the heterolytic reaction to a homolytic one because of the initial formation of RCoCl which undergoes homolysis to give a radical and a radical-like halide of the transition metal:

$$RCoCl \longrightarrow R\cdot + \cdot CoCl$$

The reaction with benzophenone, which under these conditions gives only benzpinacol, may be formulated, for example, as follows:

$$C_6H_5MgX+CoX_2 \longrightarrow C_6H_5\cdot + \cdot CoX + MgX_2$$

$$2C_6H_5COC_6H_5+2\cdot CoX \longrightarrow (C_6H_5)_2C(XCoO)-C(OCoX)(C_6H_5)_2 \xrightarrow[-2CoX_2]{2MgX_2}$$

$$\longrightarrow (C_6H_5)_2C(XMgO)-C(OMgX)(C_6H_5)_2 \xrightarrow{H_2O} (C_6H_5)_2C(HO)-C(OH)(C_6H_5)_2$$

A great variety of other types of reaction have been devised, which involve the interaction of Grignard reagents with the various nitrogen, sulphur, and other functional groups, and with combinations of the various oxygen functional groups. There are hundreds of such reactions. It may probably be stated, without the risk of making a mistake, that syntheses involving organomagnesium compounds constitute the most versatile and extensively used method of building molecules in organic chemistry. This method originated in 1900 as the result of modification and extensive development of the synthetic method of utilization of organozinc compounds, which was

discovered by A. M. Butlerov (Kazan') and worked out by his pupils A. M. Zaitsev, E. E. Wagner, S. N. Reformatsky, and others.

Organozinc Compounds. Alkyl iodides are reacted with zinc shavings to form RZnI and when salts of this type are subjected to dry distillation, liquid, air-inflammable compounds, R_2Zn, are distilled off:

$$RI + Zn \longrightarrow RZnI$$

$$2RZnI \longrightarrow R_2Zn + ZnI_2$$

It is these compounds that were chiefly used in synthesis.

Reactions of organozinc compounds quite analogous to those of organomagnesium compounds have made it possible to synthesize primary and secondary alcohols. Tertiary alcohols whose existence was predicted by Butlerov on the basis of structure theory were discovered by him by means of a synthesis involving organozinc compounds:

$$CH_3-\underset{\displaystyle Cl}{\overset{\displaystyle |}{C}}=O + ZnR_2 \longrightarrow CH_3-\underset{\displaystyle R}{\overset{\displaystyle R}{\overset{|}{\underset{|}{C}}}}-OZnCl \xrightarrow{H_2O}$$

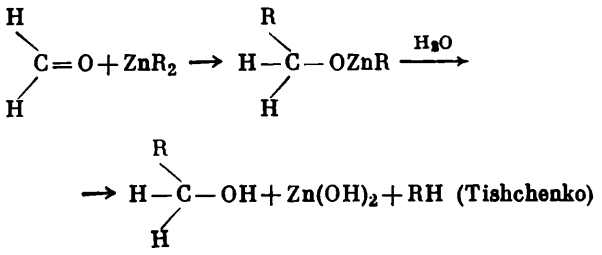
$$\longrightarrow CH_3-\underset{\displaystyle R}{\overset{\displaystyle R}{\overset{|}{\underset{|}{C}}}}-OH + Zn(OH)Cl \text{ (Butlerov)}$$

$$\underset{\displaystyle R}{\overset{\displaystyle R}{\diagdown}}\!\!>C=O + ZnR'_2 \longrightarrow R-\underset{\displaystyle R}{\overset{\displaystyle R'}{\diagdown}}\!\!>C-OZnR' \xrightarrow{H_2O}$$

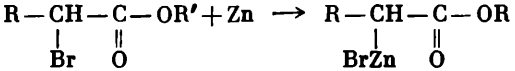
$$\longrightarrow R-\underset{\displaystyle R}{\overset{\displaystyle R'}{\diagdown}}\!\!>C-OH + Zn(OH)_2 + R'H \text{ (Zaitsev)}$$

$$R-\underset{\displaystyle H}{\overset{\displaystyle |}{C}}=O + ZnR'_2 \longrightarrow \underset{\displaystyle R\ H}{\overset{\displaystyle R'}{\diagdown}}\!\!>C-OZnR' \xrightarrow{H_2O}$$

$$\longrightarrow R-\underset{\displaystyle H}{\overset{\displaystyle R'}{\diagdown}}\!\!>C-OH + Zn(OH)_2 + R'H \text{ (Wagner)}$$

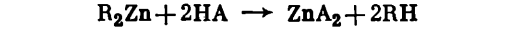


Organozinc compounds, however, are more inert than organomagnesium compounds and do not react with carbon dioxide under ordinary conditions. After the discovery of the Grignard reaction dialkylzinc compounds, which are inconvenient to handle, are hardly used at present. Compounds of the type RZnX, which are less reactive, are still employed in a limited area of application. For instance, by reacting RZnX with acid chlorides it is possible to prepare ketones in a better yield than in the case of the Grignard reaction with the same acid chlorides since the resulting ketone reacts further rather slowly. Besides, the extensive use of organozinc compounds obtained by the Reformatsky reaction



has already been considered in the case of the synthesis of β-hydroxy acids (see Volume II, page 57). Compounds of this kind, called collectively the **Reformatsky reagent,** have been isolated in a pure state by K. A. Kocheshkov.

The behaviour of organozinc compounds towards water, acids, alcohols, and amines is the same as that of organomagnesium compounds:



Organocadmium Compounds. In their properties these compounds are similar to organozinc compounds. In the synthesis of ketones from acid chlorides of carboxylic acids there is often added cadmium chloride to a Grignard reagent to convert it into RCdCl which is then treated with an acid chloride to improve the yield of the ketone.

Organometallic Compounds of Calcium, Strontium, and Barium. These compounds have been studied little. They are produced with difficulty and in low yield by the action of alkyl iodides on metallic shavings. The compounds in question are even more reactive than organomagnesium compounds.

Organoberyllium Compounds. These are made with difficulty by the interaction of the metal with alkyl halides. They are best synthesized via a Grignard reagent. Two types of compounds are known:

RBeX and R_2Be. In their properties they are closer to organoaluminium than to organomagnesium compounds.

Organomercury Compounds. In methods of preparation and properties organomercury compounds sharply differ from compounds of the other elements of Group II. They are more similar to organometallic compounds of Sn, Pb, Sb, Bi, while compounds of the alkaline-earth metals, Be, Mg, Zn, Cd more closely resemble the organometallic compounds of the alkali metals.

Organomercury compounds are classed into two groups: compounds of the general formula R_2Hg and mixed, RHgCl (organomercury salts in which any anion may take the place of Cl). These compounds can be produced by the general reaction of synthesis of organometallic compounds—by the action of a Grignard reagent on an appropriate amount of a mercury halide:

$$RMgCl + HgCl_2 \longrightarrow RHgCl + MgCl_2$$
$$2RMgCl + HgCl_2 \longrightarrow R_2Hg + 2MgCl_2$$

Compounds of the general formula RHgX are converted into R_2Hg by the **symmetrization reaction** caused by the action of a number of substances capable of binding a mercury salt into a complex or any other non-ionic compound:

$$2RHgX + 4KCN \longrightarrow R_2Hg + K_2^+[Hg(CN)_4]^{2-} + 2KX$$
$$2RHgX + 4KI \longrightarrow R_2Hg + K_2^+[HgI_4]^{2-} + 2KX$$
$$2RHgX + 2NH_3 \longrightarrow R_2Hg + [Hg(NH_3)_2]^{2+}\ 2X^-$$

The reverse conversion into RHgX is accomplished by heating a solution (e.g., in alcohol) of equivalent amounts of R_2Hg and an organic or inorganic mercury salt:

$$R_2Hg + HgX_2 \longrightarrow 2RHgX$$

The reaction goes practically to completion, and more rapidly if R = aryl or vinyl, and more slowly if R = alkyl.

Unsymmetric normal organomercury compounds of the general formula RHgR′ are also known. They are prepared by the Kharasch method through the action of a Grignard reagent on organomercury salts:

$$RHgX + R'MgX \longrightarrow RHgR' + MgX_2$$

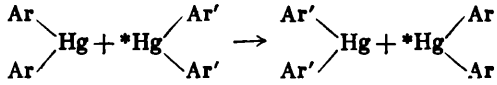
Organolithium compounds may be used instead of the Grignard reagent, or better (according to A. N. Nesmeyanov, K. A. Kocheshkov, and R. Kh. Freidlina) if RHgX is acted on in alkaline solution by $R'B(OH)_2$, $R'SnO(OH)$, $R'As(OH)_2$ and other organometallic compounds of non-transition elements, which have an acid function. For example,

$$RHgX + R'B(OH)_2 + OH^- \longrightarrow RHgR' + B(OH)_3 + X^-$$

Unsymmetric organomercury compounds are generally unstable and on standing undergo symmetrization (they do so more rapidly when heated):

$$2RHgR' \longrightarrow R_2Hg + R'_2Hg$$

They are the more stable the greater is the difference in the electronegativity of the radicals, so that compounds of the type ArHgAr' with similar aryls are the least stable and compounds of the general formula RHgCN the most stable and do not differ from organomercury salts in this respect. The ease of symmetrization of RHgR' makes it easier for us to understand the surprising fact discovered by O. A. Reutov, which consists in the rapid exchange of mercury atoms between diarylmercury molecules having ordinary mercury and its radioactive isotope:

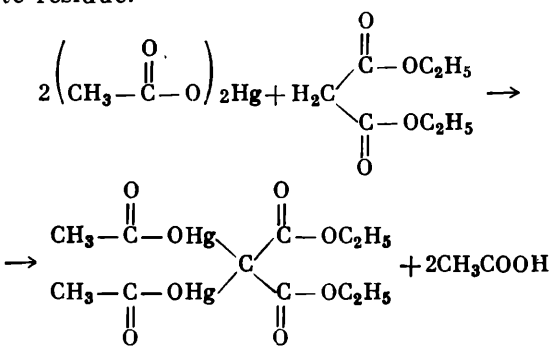


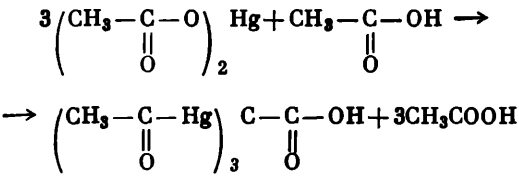
Such an exchange can provide a spontaneous symmetrization of unsymmetrical organomercury compounds of the general formula uHgR'.

Mention should also be made of the no less remarkable fact revealed by the same author—the rapid exchange of the metal of diarylmercury (and also dichlorovinylmercury) with metallic mercury, which has also been established by experiments involving radioactive metallic mercury.

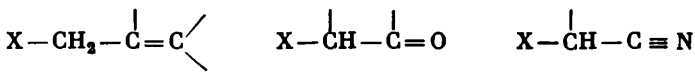
In contrast to the majority of other organometallic compounds, for which the synthesis with the aid of a Grignard reagent is the principal method, organomercury compounds can be synthesized by a number of other methods as well. We shall consider only the methods of preparation of compounds of the aliphatic series.

1. The direct replacement of a sufficiently mobile hydrogen by a HgX residue through the action of HgX_2 on YCH_3 or $Y—CH_2—Z$, where Y and Z are carbonyls, carboxyls, or the nitro group, and X is the acetate residue:

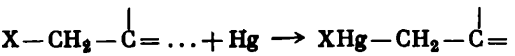




The interaction of the systems

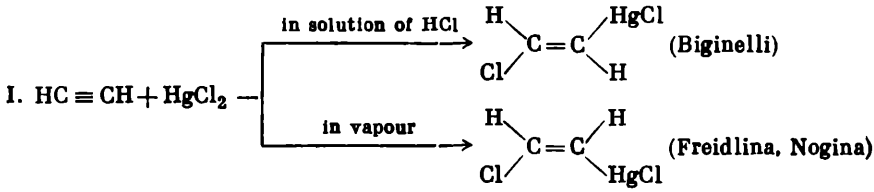


that is, allyl halides (N. N. Zinin), α-halogenocarbonyl compounds and esters of α-halogen acids (O. A. Reutov) or their nitriles (V. A. Abramov) with metallic mercury, especially on illumination:



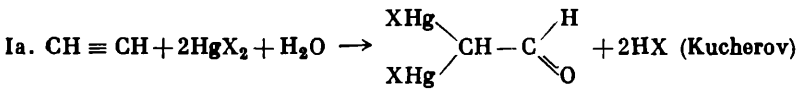
The iodides react most readily, and the chlorides least readily.

2. The addition of mercuric acetate (or, in a more limited extent, other salts) to unsaturated compounds in aqueous or alcoholic solution affords a special type of "quasi-complex" compounds of mercury:

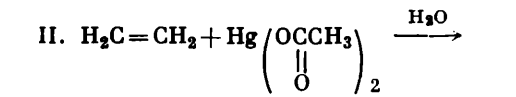


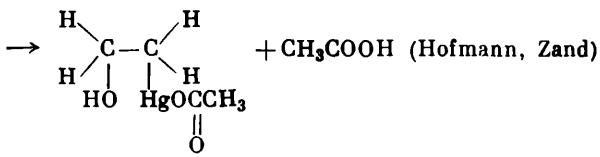
(Biginelli)

(Freidlina, Nogina)

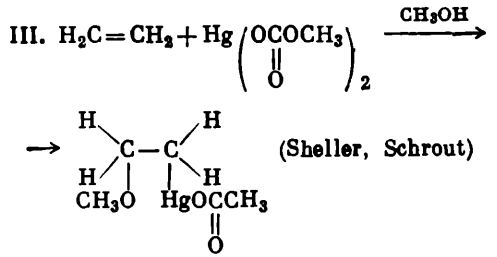


(Kucherov)

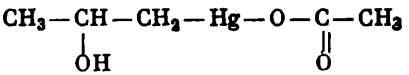




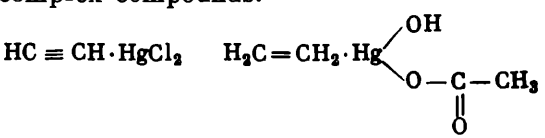
(Hofmann, Zand)



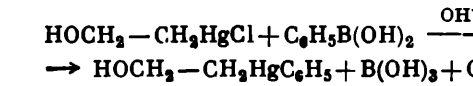
The addition of a mercury salt to unsymmetrical olefins obeys the same rules as the heterolytic addition of hydrogen halide (Markovnikov's rule), so that from propylene there is obtained the compound



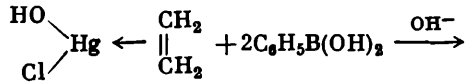
The quasi-complex (A. N. Nesmeyanov, R. Kh. Freidlina) organomercury compounds having very peculiar properties and resulting from the addition of mercury salts to acetylenes (I and Ia) and olefins (the reactions of hydroxymercuration II and alkoxymercuration III) are noted for the following specific feature: when they are acted on by reagents which attack the mercury ion and bind it into a complex (I^-, CN^-, $S_2O_3^{2-}$, etc.), an elimination reaction takes place even in the cold—mercury with its anion is eliminated and Cl, OH, or OCH_3 (for reactions I-III) are eliminated from the β-position to mercury, and in this way the olefin or acetylene is regenerated. This is reminiscent of the behaviour of π-complexes of olefins and acetylene; therefore, for some time the addition products were assigned the structure of complex compounds:



The structure of these compounds has been conclusively clarified by the works of Middleton, R. Adams and A. N. Nesmeyanov, R. Kh. Freidlina, A. E. Borisov. The last-named three authors have proved the existence of *cis-trans* isomerism in the products of addition of mercury salts to acetylene and its derivatives, which is inconsistent with the formulas of complex compounds. Moreover, they have shown that the adducts with olefins are converted by the Nesmeyanov-Kocheshkov-Freidlina method into unsymmetrical normal organomercury compounds:

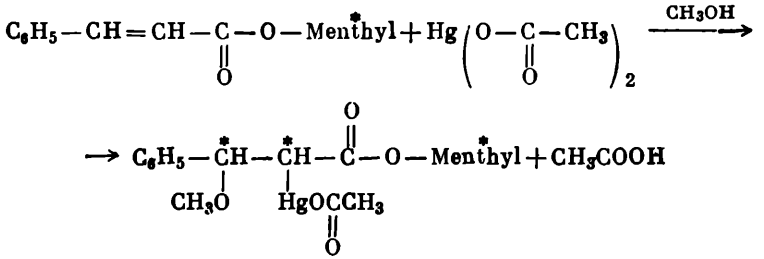


while the alternative structure with a complexed mercury atom would give, under the conditions of this reaction, diphenylmercury and ethylene (see below for the properties of quasi-complex compounds):

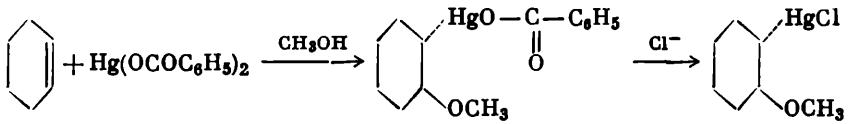


$$\longrightarrow (C_6H_5)_2Hg + CH_2=CH_2 + 2B(OH)_3 + Cl^-$$

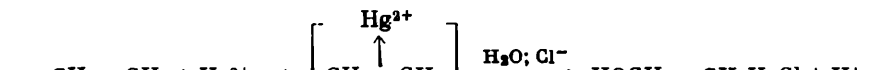
At an earlier time Marvel had isolated two diastereomers from the product resulting from the addition of a mercury salt to the L-menthyl ester of cinnamic acid, which may be most naturally accounted for by the appearance of new asymmetric centres due to the addition of the mercury salt:



O. A. Reutov and V. I. Sokolov, employing the method of quantitative calculation of molecular rotation developed by Brewster (see Volume II, page 330), have established, using the addition of a mercury salt to cyclohexene, that HgX and OCH_3 enter the *trans*-position:

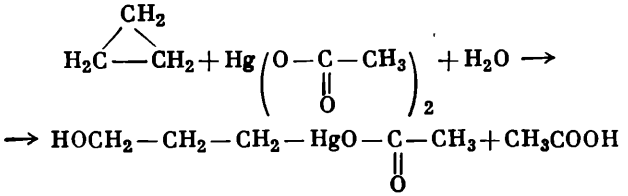


Thus, the adducts of a mercury salt and olefins (or acetylenes) are the products of an addition reaction with cleavage of the double bond. Arguments have been forwarded (Winstein) in favour of the instantaneous formation of a π-complex (the mercurinium ion) as the first unstable stage of the addition reaction:

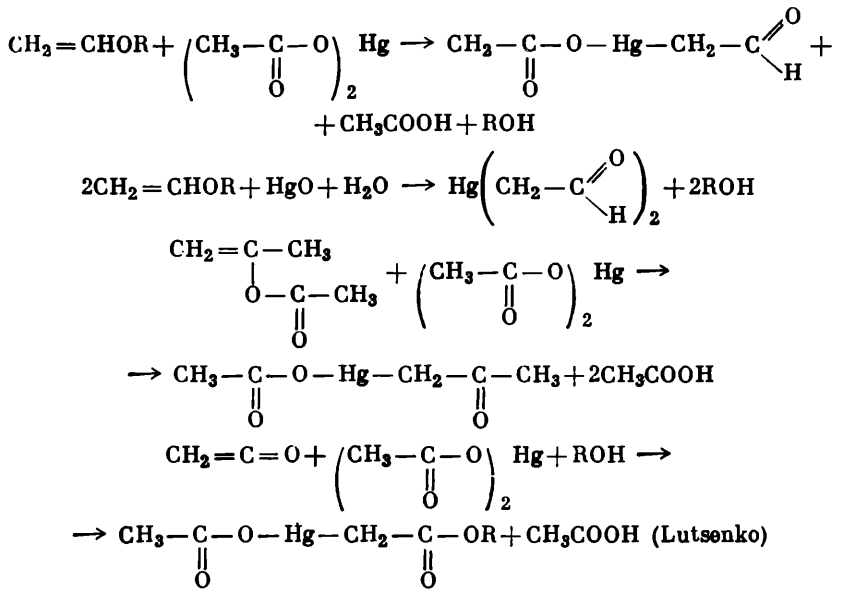


According to the data obtained by R. Ya. Levina, mercury salts open the three-membered ring and the addition reaction proceeds

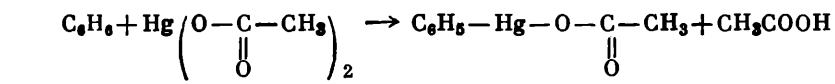
nnalogously to the addition to olefins:



The addition of mercury salts to ethers and esters of vinyl alcohol and to ketenes takes a peculiar course and leads to the mercury derivatives of aldehydes, ketones, and acids (A. N. Nesmeyanov, I. F. Lutsenko):



3. In the aromatic series, organomercury compounds are prepared most simply by direct mercuration (Dimroth); an example is the mercuration of benzene which occurs when benzene is boiled with mercuric acetate or other mercury salts:



The reaction is an electrophilic substitution reaction and, hence, is facilitated by *ortho-para* substituents, which direct mercury into the *ortho-para* positions, and is slowed down by *meta*-substituents. Aniline, for example, is mercurated in aqueous solution even at room

temperature, a mixture of *o*- and *p*-acetatemercurianilines being formed. The phenols too are readily mercurated. Many of the mercurated phenols are used as antiseptics, bactericides and agricultural fungicides.

4. The second synthetic method specific for the aromatic series is the synthesis of organomercury compounds via diazo compounds (A. N. Nesmeyanov). It consists of the action of powdered metallic copper on double salts of an aryldiazonium chloride and mercuric chloride:

$$Ar-\overset{+}{N}\equiv N\ HgCl_3^- + 2Cu \longrightarrow ArHgCl + N_2 + 2CuCl$$

$$2Ar-\overset{+}{N}\equiv N\ HgCl_3^- + 6Cu + 6NH_3 \longrightarrow Ar_2Hg + 2N_2 + 6CuCl\cdot NH_3 + Hg$$

This method can be used to prepare (from a corresponding amine) any desired isomer of an aromatic organomercury compound, while the Dimroth direct mercuration usually gives a mixture of isomers.

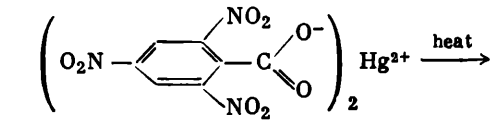
5. The reaction between ArBr and sodium amalgam affords diarylmercury (Dreher, Otto):

$$2ArBr + Na_2Hg \longrightarrow Ar_2Hg + NaBr$$

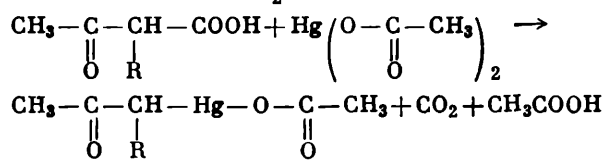
6. The action of mercuric chloride on sulphinic acids makes the residue SO_2H to be replaced by HgCl (Peters):

$$ArSO_2H + HgCl_2 \longrightarrow ArHgCl + SO_2 + HCl$$

7. Labile carboxyl groups when acted on by mercury salts are replaced by mercury:



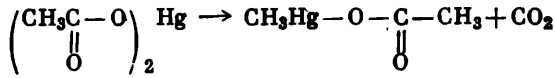
$$\longrightarrow \left(O_2N-C_6H_2(NO_2)_2-\right)_2 Hg + 2CO_2 \text{ (Kharasch)}$$



(Kharasch; Nesmeyanov and Lutsenko)

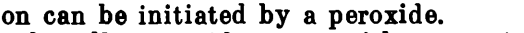
8. According to G. A. Razuvaev and Yu. A. Ol'dekop, mercuric acetate and its homologues when exposed to ultraviolet radiation decarboxylate by a free-radical mechanism, forming an alkylmercu-

ricarboxylate:

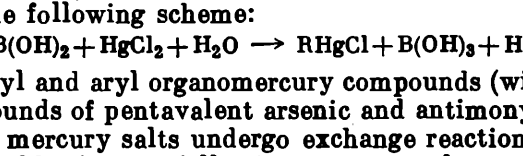


This reaction can be initiated by a peroxide.

9. Alkyl- and arylboric acids react with mercuric chloride according to the following scheme:

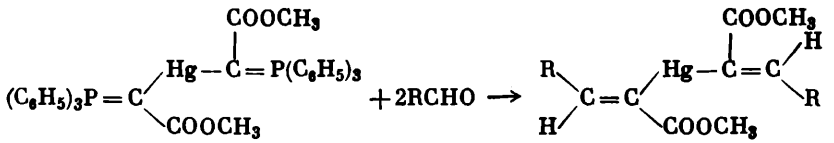


10. All alkyl and aryl organomercury compounds (with the exception of compounds of pentavalent arsenic and antimony) when made to react with mercury salts undergo exchange reactions (A. Nesmeyanov, Kocheshkov). The following are examples:



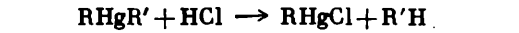
Reactions 9 and 10 when carried out in alkaline solution lead directly to R_2Hg.

Some of the vinyl compounds of mercury can be prepared with the aid of mercury-containing phosphorus ylides (N. A. Nesmeyanov, O. A. Reutov); for example,

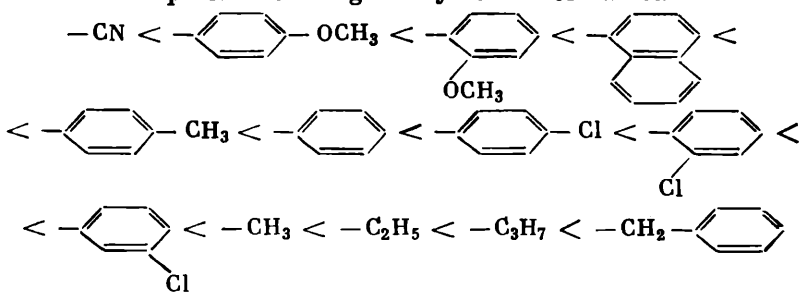


The Wittig reaction will be discussed in more detail at a later time.

Properties and Reactions of Organomercury Compounds. In unsymmetrical RHgR′ one of the radicals—the more electronegative one—is more susceptible to the attack of a proton. By investigating systematically the result of the reaction



Kharasch set up an electronegativity series for radicals:



From this series it follows that acids eliminate aromatic radicals more readily than aliphatic radicals from $RHgAr$, and that aromatic radicals containing *o,p*-directors in the *ortho*- and *para*-positions are eliminated more easily than the unsubstituted phenyl group. Thus, as regards the aromatic ring linked to mercury, the attack of H^+ is an ordinary electrophilic attack on the aromatic ring, namely on its carbon attached to mercury. With hydrohalic acids the reaction proceeds more rapidly than with other strong acids, which is accounted for by the participation of halogen in the four-membered transition state (see page 255):

$$RHgR + HCl \longrightarrow \left[\begin{array}{c} R-Hg-R \\ | \quad\; | \\ H-Cl \end{array}\right] \longrightarrow RH + RHgCl$$

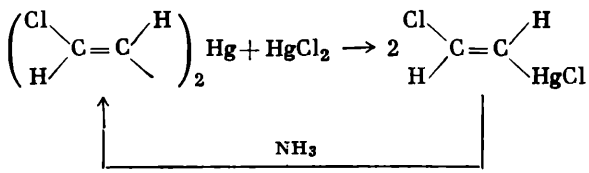
The radical in RHgCl is held now more firmly and more drastic conditions of acidolysis are required for this radical to be detached in the form of RH.

In the reaction

$$RHgR' + {}^*HgCl_2 \longrightarrow R'HgCl + R^*HgCl$$

which occurs readily on heating in solution the mercury of mercuric chloride (labelled) captures the radical R′ which is the less electronegative in the Kharasch series (N. A. Nesmeyanov and O. A. Reutov).

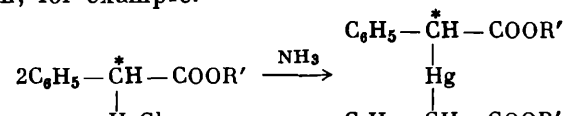
The exchange reactions of the geometric isomers of β-substituted vinyl compounds of mercury with mercuric chloride proceed, just as the reverse reaction (symmetrization), with retention of configuration (A. N. Nesmeyanov, A. E. Borisov, 1948):



Exchange reactions between R_2Hg and mercuric chloride and symmetrization reactions of the type

$$2RHgX \longrightarrow R_2Hg$$

also proceed with retention of configuration (A. N. Nesmeyanov, O. A. Reutov, I. P. Beletskaya). Of course, it applies to cases where the asymmetric radical R is attached to mercury via its asymmetric carbon atom; for example:



These were the first reactions of the S_E2 type in which their stereochemical course was proved to be the opposite to that of reactions of the S_N2 type. In carrying out some reactions involving the exchange of mercury in a strongly solvating nucleophilic solvent (dimethylsulphoxide) it turned out that they proceeded by an S_E1 mechanism that had never been observed before, i.e., with the preliminary slow ionization at the C—Hg bond and racemization (O. Reutov, I. Beletskaya):

$$\left(-\overset{\diagdown}{\underset{\diagup}{C}}-\right)_2 Hg \overset{\text{slow}}{\rightleftharpoons} -\overset{\diagdown}{\underset{\diagup}{C}}: + \overset{+}{H}gC-$$

$$-\overset{\diagdown}{\underset{\diagup}{C}}: + HgCl_2 \xrightarrow{\text{rapid}} -\overset{\diagdown}{\underset{\diagup}{C}}-HgCl + Cl^-$$

Lower dialkylmercury compounds are liquids which distil off without decomposition; they are very poisonous and have a slightly unpleasant smell. Especially nauseating is the smell of the lower alkylmercurichlorides which are solids with a mobile halogen easily replaceable by other anions. Diarylmercury compounds are solids which have a lower melting point than arylmercury chlorides [for example, $(C_6H_5)_2Hg$ melts at 125°C, and C_6H_5HgCl at 272°C] and are more soluble in organic solvents than the latter.

When a dialkylmercury compound is made to react with concentrated mineral acids (but not weak acids or water), one of the radicals is split off from it:

$$R_2Hg + HCl \longrightarrow RHgCl + RH$$

Mercury diaryls react even more readily with hydrochloric acid, the halogens and mercury salts than mercury dialkyls.

The reduction of mercury dialkyls with nascent hydrogen (NaHg + H_2O; Zn + HCl in ethanol) or with hydrogen at a high temperature and pressure (G. A. Razuvaev) liberates metallic mercury and forms a hydrocarbon:

$$R_2Hg + 2H \longrightarrow 2RH + Hg$$

A halogen eliminates both radicals, one after the other, from the mercury dialkyl:

$$R_2Hg + I_2 \longrightarrow RHgI + RI$$

$$RHgI + I_2 \longrightarrow HgI_2 + RI$$

With ordinary organomercury compounds, additions at a carbonyl group or exchanges with alkyl halides and any other reactions similar to the reactions of organomagnesium compounds do not occur at all.

Reutov and Beletskaya have found, however, that with "nucleophilic assistance" in a strongly ionizing aprotic solvent, say, in dimethylsulphoxide, the mercury in mercury diaryls is exchanged for

a radical, such as the triarylmethyl radical. Nucleophilic assistance is the simultaneous attack on the mercury of an anion similar to the iodide ion:

$$(C_6H_5)_2Hg + ClC(C_6H_5)_3 \longrightarrow C_6H_5C(C_6H_5)_3 + C_6H_5HgI + Cl^-$$
$$\underset{I^-}{}$$

The only two exchange reactions in which organomercury compounds are widely used in the synthesis of organometallic compounds are exchange reactions with metals and metal halides. All non-transition metals, which are considerably less noble than mercury, enter into exchange reactions, namely: Li, Na, K, etc.; Mg, Zn, Cd, Al, Ga, In, Tl, Sn, Sb, Bi. For example:

$$R_2Hg + Zn \longrightarrow R_2Zn + Hg$$
$$2R_2Hg + AsCl_3 \longrightarrow R_2AsCl + 2RHgCl$$
$$Ar_2Hg + ICl_3 \longrightarrow ArICl_2 + ArHgCl$$
$$Ar_2Hg + ArICl_2 \longrightarrow Ar_2ICl + ArHgCl$$

The halides of alkali and alkaline-earth metals do not enter into such reactions, but the halides of other non-transition metals do so more or less difficultly.

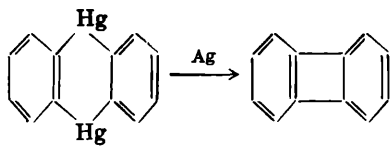
Both exchange reactions were historically important methods, with the aid of which many individual organometallic compounds of non-transition elements were prepared for the first time.

While studying such metal exchange reactions in *cis*- and *trans*-isomers of β-chlorovinylmercurichloride and bis-β-chlorovinylmercury, A. N. Nesmeyanov and A. E. Borisov established the rule: electrophilic and homolytic substitutions at the olefinic carbon atom proceed with retention of configuration (*cis*- or *trans*-).

When mercury diaryls are heated with transition metals (Ag, Pd, Pt, etc.), a diaryl is formed (Razuvaev):

$$Ar_2Hg \overset{Pd}{\rightleftharpoons} Ar-Ar + Hg$$

Using this reaction, Wittig prepared *o*-diphenylene:



Quite different properties are exhibited by **quasi-complex organomercury compounds.** As stated earlier, these are the adducts of mercury salts with olefins or acetylenes, which have the structure of β-hydroxy, β-alkoxy, β-halogen, etc., substituted alkyl- or alkenylorganomercury compounds. The adducts of olefins react, like other organomercury compounds, only when reduced with sodium

amalgam, and the adducts of acetylene do so in reactions with the halogens, metals and metal halides.

The most characteristic reaction of quasi-complex compounds is the **β-elimination** (see page 263), which begins when the β-substituent and the mercury atom are attacked and leads to the evolution of an olefin (or acetylene, respectively) and mercury in the form of an inorganic compound:

$$\underset{H^+}{HO-CH_2CH_2-HgCl} \longrightarrow H-\underset{H}{O}+CH_2=CH_2+\underset{Cl^-}{HgCl_2}$$

$$HO-CH_2CH_2-HgCl+3I^- \longrightarrow CH_2=CH_2+HgI_3^-+OH^-+Cl^-$$

$$Cl-CH=CH-HgCl+3I^- \longrightarrow HC\equiv CH+HgI_3^-+2Cl^-$$

An analogous course is taken by reactions with CN^-, $S_2O_3^{2-}$, etc. Thus, reagents that usually symmetrize organomercury salts destroy quasi-complex compounds. The latter can be symmetrized only by the action of ammonia:

$$2Cl-CH=CH-HgCl+2NH_3 \longrightarrow (ClCH=CH)_2Hg+Hg(NH_3)_2Cl_2$$

Formally, these elimination reactions may be likened to reactions of 1,4-addition to conjugated C=C—C=C systems. Indeed, for example, the cleavage of ethanolmercurichloride by hydrochloric acid is represented schematically as follows:

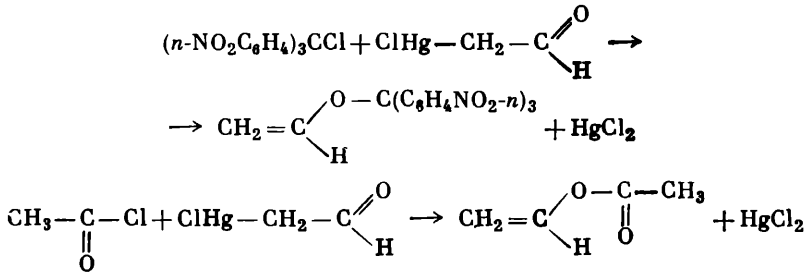
$$\underset{H^+}{\overset{1}{HO}-\overset{2}{CH_2}-\overset{3}{CH_2}-\underset{Cl^-}{\overset{4}{HgCl}}} \longrightarrow HOH+CH_2=CH_2+HgCl_2$$

The σ-bonds printed in bold face play a part analogous to that of the conjugated π-bonds of the diene system (σ,σ-conjugation, or hyperconjugation). The attack of H^+ and Cl^- is directed to the first and fourth atoms of the conjugated system. Just as in the C=C—C=C system, as a result of 1,4-addition the bonds 1,2 and 3,4 are broken and a π-bond is formed between carbon atoms 2 and 3. The above-described addition of mercury salts to vinyl ethers and esters results (after the anion has been replaced) in the formation of α-halogenomercuraldehydes and ketones which are also specific in their reactions. In contrast to the alkyl and aryl compounds, the mercury in the α-position to the carbonyl group is "readily mobile" and enters into an exchange reaction with organic and inorganic halogen derivatives, the reactions proceeding both without and (often) with transfer of the reaction centre.

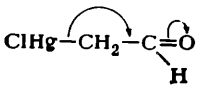
(a) Reactions without transfer of the reaction centre:

$$(C_6H_5)_3CCl+ClHg-CH_2-C\overset{O}{\underset{H}{<}} \longrightarrow (C_6H_5)_3C-CH_2-C\overset{O}{\underset{H}{<}}+HgCl_2$$

(b) Reactions with transfer of the reaction centre (A. N. Nesmeyanov, I. F. Lutsenko, E. G. Perevalova):

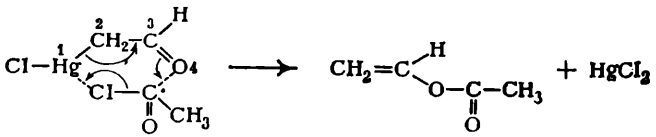


Reactions involving the transfer of the reaction centre proceed as electrophilic attacks on oxygen (and not on carbon) and yield derivatives (acetyl, in this case) of the tautomeric form of the carbonyl compound, although, in contrast to the carbonyl compound itself, its mercury derivative does not exhibit tautomerism, i.e., in the system

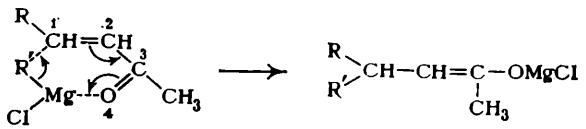


the attack at oxygen is facilitated by the simultaneous supply of electrons due to the readily polarizable Hg—C bond.

A reaction of this type may formally be regarded as a 1,4-addition at a σ,π-conjugated, i.e., hyperconjugated, system of bonds (A. Nesmeyanov):



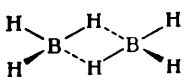
and, analogously,



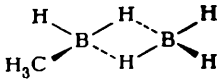
12.4. Group III of the Periodic System

Organoboron Compounds. Inorganic and organic compounds of boron have been studied especially intensively in the recent years, and the variety of the types of compounds known increases rapidly.

Boron hydrides, both containing substituting organic radicals and pure hydrides, are interesting by their bridging hydrogen bonds, e.g.,

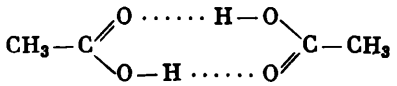


Diborane



Methyldiborane

The hydrogen atoms of these hydrogen bridges are fully symmetric with respect to both boron atoms, a feature that differentiates such bridges from ordinary hydrogen bridges, say, those present in acetic acid



where the distances from the hydrogen atoms in the dimer ring to the hydroxyl oxygen of "its" molecule and the carbonyl oxygen of the "foreign" molecule are sharply different. In diborane, four electrons belong to four atoms (two boron and two hydrogen atoms) and form four-centre orbitals.

The following boron hydrides are also known: B_4H_{10}, B_5H_9, B_5H_{11}, B_8H_{12}, B_9H_{13} and, finally, decaborane, $B_{10}H_{14}$, which is the most stable one. Some of them are known to have alkyl and other substituted derivatives which are obtained by the Schlessinger method through the interaction of boranes with boron trialkyls. The different behaviour of diborane and decaborane towards the Grignard reagent is interesting (Wiberg):

$$B_2H_6 + RMgBr \longrightarrow RB_2H_5 + HMgBr$$
$$B_{10}H_{14} + RMgBr \longrightarrow B_{10}H_{13}MgBr + RH$$

By reacting $B_{10}H_{13}MgBr$ with alkyl halides it is also possible to prepare alkyl decaboranes (Wiberg):

$$B_{10}H_{13}MgBr + RBr \longrightarrow RB_{10}H_{13} + MgBr_2$$

The structure of boron hydrides (see Figs. 12.2, 12.3, and 12.4) and their derivatives is interesting exactly because it contradicts (just as a number of other structures of organoelement compounds) the long-established rules of classical structure theory and provides for further improvement of our structural conceptions.

Diborane and alkyldiboranes add on (due to B—H bonds) to olefins and acetylenes by a reaction of the following type (Herd, Brown):

$$B_2H_6 + 6RCH=CH_2 \longrightarrow 2(RCH_2-CH_2-)_3B$$
$$B_2(CH_3)_2H_4 + 4RCH=CH_2 \longrightarrow 2(RCH_2-CH_2-)_2BCH_3$$

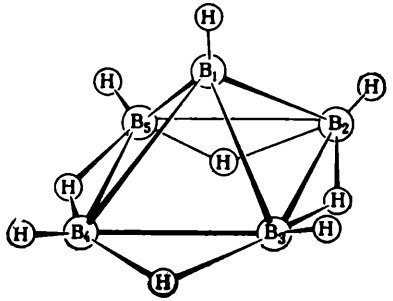


Fig. 12.2.
The structure of pentaborane B_5H_9.

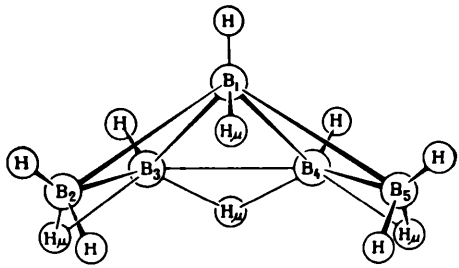


Fig. 12.3.
The structure of pentaborane B_5H_{11}.

The addition here seems to invariably proceed against Markovnikov's rule. This is because the hydrogen in boron hydrides is more electronegative and splits off as the hydride ion H^-, and the boron is more positive, so that Markovnikov's rule (see Volume I, page 336) is observed actually rather than formally.

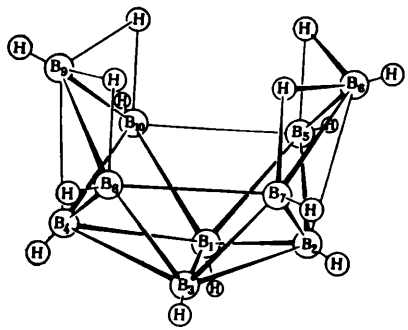


Fig. 12.4:
The structure of decaborane $B_{10}H_{14}$.

For organoboron compounds to be synthesized, instead of boron hydrides, which are spontaneously inflammable in air and very poisonous, BCl_3 may be used for the reaction with olefins in the presence of metallic aluminium:

$$RCH=CH_2+HBCl_2 \longrightarrow$$
$$\longrightarrow RCH_2-CH_2BCl_2$$

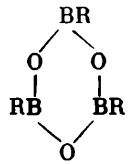
The reaction apparently proceeds via the preliminary formation of $HBCl_2$ and its addition to the olefin.

The reaction widely used for the synthesis of organoboron compounds is the interaction of boron trihalide (Krause) or borates (E. Khotinsky) with organolithium compounds or the Grignard reagent:

$$BX_3+3RMgBr \longrightarrow R_3B+3Mg\begin{matrix}Br\\X\end{matrix}$$

The same route can be used to prepare compounds, such as $R_2B(OCH_3)$, $RBCl_2$ and R_2BCl, which on hydrolysis give alkyl- and dialkylboric acids, $RB(OH)_2$ and $R_2B(OH)$, which are even weaker than boric acid and which rather easily lose alkyls when oxi-

dized by atmospheric oxygen and when acted on by a number of metal halides ($HgCl_2$, $CuCl_2$) but not by acids. Alkylboric acids when dried or on elimination of the elements of water by chemical means form interesting trimeric cyclic anhydrides



When the complex salt KBF_4 is treated with the Grignard reagent RMgBr, the compound R_3B is obtained in the case of an aliphatic radical R; with the aromatic ArMgBr the reaction proceeds by the following scheme (A. N. Nesmeyanov, V. A. Sazonova)

$$KBF_4 + 4ArMgBr \longrightarrow K^+ {}^-BAr_4 + 2MgF_2 + 2MgBr_2$$

and salts of alkali metals with the tetraarylboron anion are obtained. These salts were first prepared by Wittig by means of the reaction:

$$BAr_3 + ArLi \longrightarrow Li^+ {}^-BAr_4$$

Here $(Ar:)_3B$ which has a sextet of electrons about boron tends to expand it to an octet and captures the radical Ar: with a pair of electrons from Li:Ar, leaving the lithium as a cation. As a result, an octet of electrons is formed around the boron which thus acquires the negative charge of the anion. Salts of this type are excellent reagents for detection of K, Pb, and Cs since they form practically water-insoluble salts with their cations.

Compounds of the type R_3B are capable of participating in the following reactions because of the same tendency:

$$R_3B + :NR'_3 \longrightarrow R_3\bar{B} : \overset{+}{N}R'_3$$

$$R_3B + NaOH \longrightarrow R_3\bar{B} : OH + Na^+$$

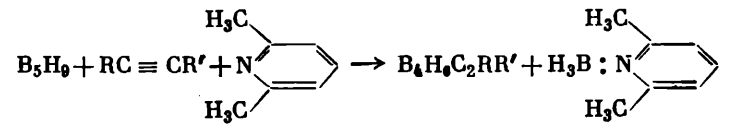
$$R_3B + 2Na\cdot \longrightarrow [R_3B : Na]^- \; Na^+$$

In the compound $R_3\bar{B}:\overset{+}{N}R'_3$ the bond $\bar{B}:\overset{+}{N}$ must be regarded as a semipolar bond because, apart from a covalent pair of electrons, the atoms are bound by their full (ionic) opposite charge formed after one neutral molecule gives a pair of electrons to another neutral molecule for this pair of electron to be shared between them. But in the anion $R_3\bar{B}$:OH the B—O bond, in spite of the fact that it is formed analogously, is now an ordinary covalent bond since the oxygen does not bear a formal (full) charge opposite to the charge that has arisen on the boron atom (OH^- came with a negative charge and lost it because its electron pair is shared with the boron).

The salt $R_4B^-M^+$ was called the **at-complex** by Wittig. It may also be called the **reversed onium compound** since the method of its formation is approximately opposite to the formation of onium (e.g., ammonium) cations:

$$R_3B + \overset{-}{R}\overset{+}{N}a \longrightarrow R_4B^- \; Na^+$$
$$R_3N + RCl \longrightarrow R_4N^+ \; Cl^-$$

In 1962 Onak, Williams and Weiss discovered the reaction of pentaborane with homologues of acetylene, which proceeds according to the equation:



Such organoboron compounds were assigned the structure shown in Fig. 12.5 on the basis of NMR spectra. In this way, there was discovered the first of a series of stable aromatic **carboranes** with polyhedral molecules of the general formula $B_nC_2H_{n+2}$. This was followed by the discovery of the other members of the series (see Fig. 12.6). The carboranes that have been most thoroughly studied are three stable decacarboranes which are very interesting by their properties: *ortho*-(1,2-), *meta*-(1,7-), and *para*-(1,12-)decacarboranes shown in Fig. 12.7. Just as in Fig. 12.6, each of the boron and carbon atoms in these structures carries one hydrogen atom not shown in Fig. 12.7. The first of these decacarboranes (the *ortho* arrangement of acetylene carbon atoms) was discovered at about the same time (1963) by L. I. Zakharkin, V. I. Stanko and coworkers (USSR), who gave the name **barene** to it, and by Fein (USA) who named it **carborane-10.** This compound contains 10 boron atoms and two carbon atoms arranged at the vertices of an icosahedron.

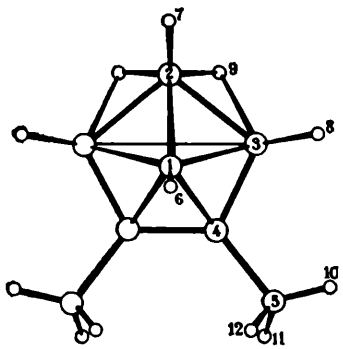


Fig. 12.5.
The structure of dimethyltetracarborane of the composition $B_4H_6C_2(CH_3)_2$.

Barene (*o*-carborane-10, or 1,2-carborane-10) is prepared by heating (up to about 90°C) complexes of decaborane, $B_{10}H_{14}L_2$, with acetylene, where L is a ligand of the acetonitrile or diethyl sulphide type. If it is heated for 24 hours up to 465-500°C, it isomerizes to *m*-carborane-10 (or 1,7-carborane-10). When *m*-carborane-10 is heated up to 615°C, *p*-carborane-10 (1,12-carborane-10) is obtained in

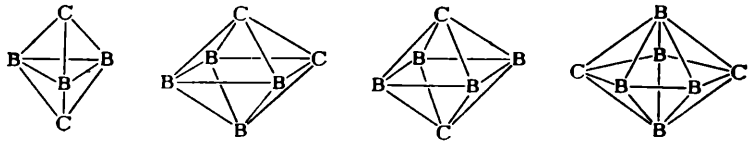


Fig. 12.6.
The structure of carboranes of the general formula $B_nC_2H_{n+2}$. (Each of the boron and carbon atoms carries one hydrogen not shown here.)

6-percent yield. All the three compounds are exceedingly thermally stable and are also resistant to oxidation and to the action of acids. The most thoroughly studied of these is barene.

According to X-ray structural data the C—C distance in barene is even greater than that in saturated hydrocarbons. When the compound is allowed to react with alkyllithium, the hydrogen atoms at

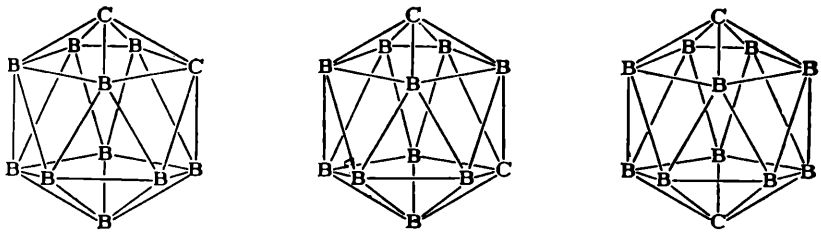


Fig. 12.7.
The structure of decacarboranes, $B_{10}H_{10}C_2H_2$:
a—1,2-carborane-10 (m.p. 287-288°C); b—1,7-carborane-10 (m.p. 266-269°C); c—1,12-carborane-10 (m.p. 259-261°C).

the former acetylene carbons are replaced by lithium atoms (Zakharkin, Stanko). This organolithium compound can be subjected to reactions typical of organolithium compounds: alkylation with RBr; carboxylation with the aid of CO_2; addition of an aldehyde; addition of ethylene oxide with the formation of alcohols; reactions with salts of metals leading to metal derivatives (O. Yu. Okhlobystin), etc. The replacement by sodium can be effected through the action of carborane-10 on sodamide in liquid ammonia, and the replacement by MgBr, through the action of C_2H_5MgBr (Heying, Ager, Clark et al., Zakharkin, Stanko et al.).

When barene is treated with an alcoholic solution of potassium hydroxide, one boron atom and two protons are eliminated and a

peculiar anion, $B_9C_2H_{11}^{2-}$ (known as the **dicarbollide anion**) is formed (Fig. 12.8*a*). This anion, as established by Hawthorne, can form sandwich compounds (page 129) with transition metals (Fig. 12.8*b* and *c*). It is possible to replace one or more hydrogen atoms attached

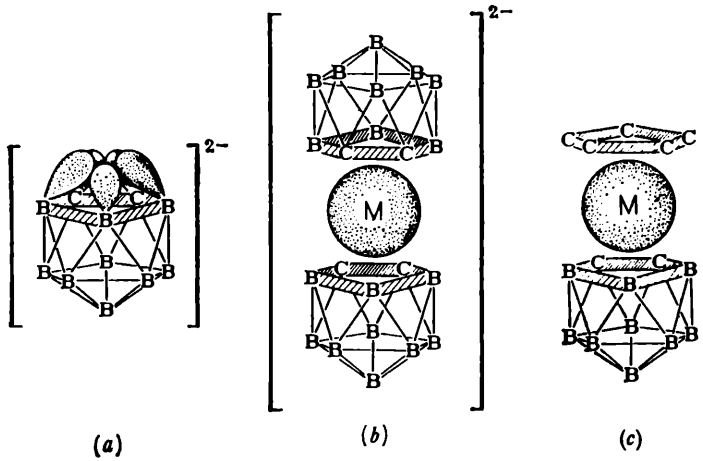


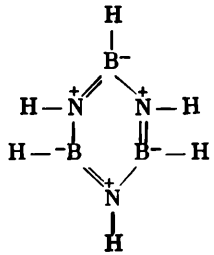
Fig. 12.8.
The structure of the dicarbollide anion, $B_9C_2H_{11}^{2-}$, and of the compounds formed by this anion with metals:
a—anion; *b*—sandwich structure of a complex with a transition metal; *c*—dicarbollide-cyclopentadienide of metal M.

to boron in barene by chlorine atoms through chlorination in the light; such a **chlorocarborane** has but a slightly mobile halogen.

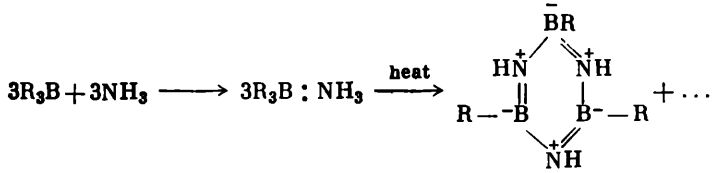
In general, carboranes are purely aromatic systems with a low energy level, which have electron-attracting properties and are bound into a single entity by multicentre electronic orbitals. Their structure cannot be described on the basis of the classical Butlerov theory of structure, making use of tetravalent carbons and trivalent boron atoms, which, by the way, occupy identically linked symmetric positions in carborane. Carboranes may be regarded as belonging to one of the most striking types of compounds which are beyond the scope of classical structural schemes. Other such compounds are diborane and other boron hydrides and also the dimers of trimethylaluminium (see below) and sandwich complexes of transition metals.

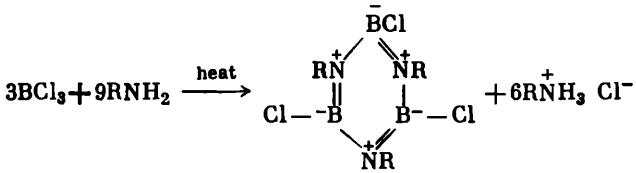
An interesting type of an inorganic compound of boron, which forms organic derivatives with R—N or R—B bonds, is **borazole**

("inorganic benzene"):



The organic derivatives of borazole can be made by the following reactions:





In this way it is possible to synthesize six-membered heterocycles with alternating B and O or B and S atoms, which have been extensively studied by B. M. Mikhailov.

Organoaluminium Compounds. Owing to the discovery by Ziegler of the reaction of direct synthesis of trialkyl compounds of aluminium from olefins, hydrogen and the finely divided metal

$$6CH_2=CH_2+3H_2+2Al \longrightarrow 2(C_2H_5)_3Al$$

organoaluminium compounds become increasingly important in industry, especially in the polymerization of olefins (see Volume I, page 346).

The following types of organoaluminium compounds are known:

$$RAlH_2, \quad R_2AlH, \quad R_3Al$$

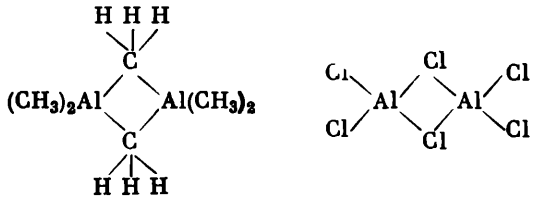
$$RAlCl_2, \quad R_2AlCl, \quad AlCl_3$$

$$[R_4Al]^- Li^+, \quad [R_3AlH]^- Li^+, \quad [R_2AlH_2]^- Li^+, \quad [RAlH_3]^- Li^+, \quad [AlH_4]^- Li^+$$

Organoaluminium compounds with the lower alkyls (CH_3, C_2H_5) are liquids which are spontaneously flammable in air; the salt-like compounds (the lower line) are solids.

The compounds $RAlH_2$ and R_2AlH are also obtained by the Ziegler reaction from pure finely dispersed aluminium, hydrogen, and an olefin; $RAlCl_2$ and R_2AlCl can be produced by the interaction of R_3Al with $AlCl_3$ or by the action of RCl on metallic aluminium in an autoclave.

One of the sharp contradictions to the foundations of structure theory and carbon tetravalency, which are generally strictly observed in saturated compounds, is the dimeric character of trimethylaluminium, whose molecular weight in the vapour state corresponds to the molecular formula $(CH_3)_6Al_2$. The structure of this compound has been found by means of physical methods to be similar to the structure of Al_2Cl_6, with methyl bridges linking aluminium atoms:



Thus, in certain rare cases the carbon (of the methyl group) links five atoms without expanding its electron shell, i.e., without changing its valency in the ordinary sense of the word. In this formula each valency bond no longer represents a pair of electrons but only the fact of direct bonding of the atoms.

Organoaluminium compounds are decomposed vigorously not only by acids but also by water and alcohols:

$$AlR_3 + 3H_2O \longrightarrow 3RH + Al(OH)_3$$

Carbon dioxide reacts with an ethereal solution of trialkylaluminiums at a temperature of 20-100°C (under pressure) with the formation of $R_2AlOC(O)R$. The second alkyl enters into reaction only at 180-200°C (L. I. Zakharkin, V. V. Gavrilenko).

Trialkylaluminium reacts vigorously also with carbonyl compounds, but the ability to reduce the latter, which is displayed but very slightly by organomagnesium compounds, is exhibited considerably more strongly by organoaluminium compounds and makes them less suitable for Grignard syntheses. But they possess the remarkable property of adding on to olefins (Ziegler), being equivalent to boron alkyls in this respect:

$$R_3Al + 3CH_2=CH_2 \longrightarrow (RCH_2CH_2)_3Al$$

Since the resulting new organoaluminium compound is also capable of adding on to olefins, the reaction does not stop at the first stage shown and, if there is excess of the olefin, goes on until high-molecular-weight compounds are formed:

$$(RCH_2CH_2)_3Al + 3CH_2=CH_2 \longrightarrow (RCH_2CH_2CH_2CH_2)_3Al, \text{ etc.}$$

The overall scheme is as follows:

$$R_3Al + 3nCH_2=CH_2 \longrightarrow [R(CH_2CH_2)_n]_3Al \xrightarrow{3H_2O} \longrightarrow 3R(CH_2-CH_2)_nH + Al(OH)_3$$

Organoaluminium compounds can be used for reactions with the corresponding halides to synthesize the organometallic compounds of heavy metals. Organoaluminium compounds are oxidized by oxygen to alkoxides.

Aromatic triarylaluminiums are conveniently prepared by heating mercury diaryls with metallic aluminium:

$$3Ar_2Hg + 2Al \longrightarrow 2Ar_3 + 2Al + 3Hg$$

Organometallic Compounds of Other Group III Metals. Scandium, yttrium, and rare-earth elements do not form ordinary organometallic alkyl and aryl compounds. Gallium, indium, and thallium form all types of such compounds: RMX_2, R_2MX, and R_3M, the starting materials being MCl_3 and RLi or RMgX. Organothallium compounds of the types $RTlX_2$ and R_2TlX are similar to organomercury compounds in certain respects (methods of synthesis and inertness). They are stable towards water and in air and salt-like, and have high-melting points. Aromatic organothallium compounds can be prepared via diazo compounds (A. N. Nesmeyanov, L. G. Makarova) or by the direct action of thallium butyrate on aromatic compounds, the latter reaction known as the **thallation reaction** (K. A. Kocheshkov). In compounds of the type R_3Tl, which have been obtained by Groll from R_2TlCl and RLi, one of the radicals is highly active. It is eliminated even by the action of weak acids or oxygen. Compounds of the general formula $RTlX_2$ are capable of disproportionating into R_2TlX (the most stable type) and TlX_3.

12.5. Group IV of the Periodic System

Organosilicon Compounds. The organic compounds of silicon were first prepared by Ladenburg and Friedel and extensively studied by Kipping. However, they became commercially important only after the investigations carried out by K. A. Andrianov.

Below are given the known types of organosilicon compounds and their names:

$RSiH_3$	$RSiCl_3$	$RSi(OCH_3)_3$
Alkylsilane	Alkyltrichlorosilane	Alkyltrimethoxysilane
R_2SiH_2	R_2SiCl_2	$R_2Si(OCH_3)_2$
Dialkylsilane	Dialkyldichlorosilane	Dialkyldimethoxysilane
R_3SiH	R_3SiCl	$R_3Si(OCH_3)$
Trialkylsilane	Trialkylchlorosilane	Trialkylmethoxysilane
R_4Si		
Tetraalkylsilane		

Alkylchlorosilanes and arylchlorosilanes and also tetraalkyl- and tetraarylsilanes can be made by the action of a Grignard reagent on silicon tetrachloride. Alkoxy- and, in particular, methoxyalkylsilanes, are obtained by the action of a Grignard reagent on the corresponding ester of orthosilicic acid, say, $Si(OCH_3)_4$, the reaction of RCl with magnesium being carried out directly in the solution of orthosilicate ester (Andrianov). Alkylsilanes and arylsilanes can be prepared by reducing alkylchlorosilanes or arylchlorosilanes, say, with lithium aluminium hydride.

Besides, silanes can add on to olefins with cleavage of the Si—H bond. Thus, for synthesis of alkyl derivatives of silicon, use may be made of $HSiCl_3$ or an alkylsilane containing a Si—H group, which are added to olefins. For example,

$$HSiCl_3 + CH_2=CH_2 \longrightarrow C_2H_5-SiCl_3$$

This reaction may also proceed as a telomerization reaction (Freidlina, Chukovskaya):

$$HSiCl_3 + \text{initiator} \longrightarrow \cdot SiCl_3$$

$$SiCl_3\cdot + CH_2=CH_2 \longrightarrow Cl_3SiCH_2-CH_2\cdot$$

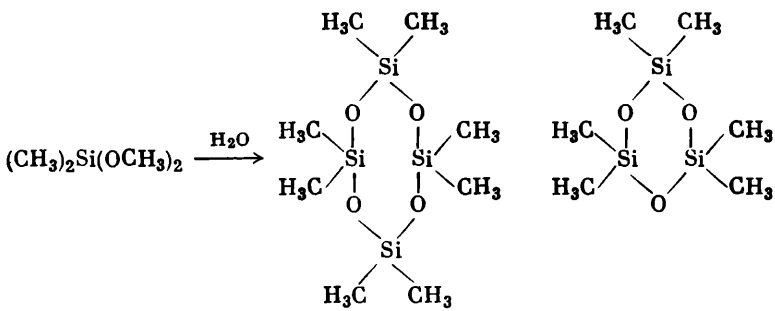
$$Cl_3SiCH_2-CH_2\cdot + CH_2=CH_2 \longrightarrow Cl_3SiCH_2CH_2CH_2CH_2\cdot$$

$$Cl_3SiCH_2CH_2CH_2CH_2\cdot + HSiCl_3 \longrightarrow Cl_3SiCH_2CH_2CH_2CH_3 + \cdot SiCl_3 \quad \text{(continues the chain)}$$

It is characteristic that dimethyldichlorosilane, $(CH_3)_2SiCl_2$, and dimethyldimethoxysilane, $(CH_3)_2Si(OCH_3)_2$ can be converted by hydrolysis into high-molecular-weight products—**polysiloxanes** (the Si—O—Si linkage), which have a number of valuable properties:

$$n(CH_3)_2Si(OCH_3)_2 \xrightarrow{H_2O} HO-\left[\begin{array}{c}CH_3\\|\\Si\\|\\CH_3\end{array}-O-\begin{array}{c}CH_3\\|\\Si\\|\\CH_3\end{array}\right]_{n-1}-OH$$

Apart from linear high-molecular-weight compounds, dimethoxysilanes readily form stable eight-membered cyclic tetramers and the less stable six-membered trimers:



The trimers can be readily converted into linear high-molecular-weight compounds.

Polysiloxanes find wide application for the preparation of a thermally stable electric insulator, synthetic rubbers, lubricating oils, etc.

Dimethyldichlorosilane, which is the necessary starting material, is prepared by the action of methyl chloride on metallic silicon (in the form of an alloy with copper; Rochow):

$$2CH_3Cl + Si \longrightarrow (CH_3)_2SiCl_2$$

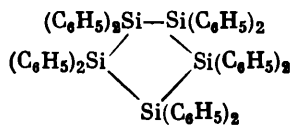
Siloxane resins with radicals other than methyl can also be produced.

In his time Kipping directed his efforts for preparation of silicon analogues of compounds with a carbon chain and did succeed in synthesizing and studying compounds of the following types:

$$(CH_3)_3Si-Si(CH_3)_3$$

$$(CH_3)_3Si-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{Si}}}}-Si(CH_3)_3 \qquad (CH_3)_3Si-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{Si}}}}-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{Si}}}}-Si(CH_3)_3, \text{ etc.}$$

including nonasilanes, and also stable cyclic structures of the type:



with four, five, and six members in the ring.

The first members of the series can be obtained by the Wurtz reaction:

$$2R_3SiCl + 2Na \longrightarrow R_3Si-SiR_3$$

or by the Kraus method, in liquid ammonia:

$$R_3SiCl + 2Li \longrightarrow R_3SiLi + LiCl$$

$$R_3SiLi + R_3SiCl \longrightarrow R_3Si-SiR_3 + LiCl$$

The —Si—Si—Si— skeletons have proved to be unstable in air and to the action of alkalis, and substances of this type have not found application. On the contrary, skeletons of the type $-O-\underset{|}{Si}-$

$-O-\underset{|}{Si}-O-\underset{|}{Si}-O-$, which are the basic structural units of silicates, both natural and artificial (glass), have become commercially important in the form of their organic derivatives due to the works of Andrianov. Compounds of the following types have been obtained

in recent years:

$$(CH_3)_3SiNa \quad \text{and} \quad (CH_3)_3SiMgCl$$

which are, to a certain extent, similar to organosodium and organomagnesium compounds. They have been used as starting materials (Razuvaev) for the synthesis of many analogues of organometallic compounds with a silicon-metal bond, for example, $[(CH_3)_3Si]_2Hg$, $[(CH_3)_3Si]_4Sn$.

Organogermanium Compounds. Organogermanium compounds which were recently rather intensively studied have not yet found application. The investigation of organogermanium compounds was begun by Kraus, Orndorf, and Dennis.

At present, the following types of compounds with a germanium atom $\left(X = \text{halogen}, \frac{1}{2}O, OH, \text{etc.}\right)$ are known:

$RGeH_3$	$RGeX_3$	
R_2GeH_2	R_2GeX_2	R_2GeNa_2
R_3GeH	R_3GeX	R_3GeNa
R_4Ge		

and also **polygermanes,** for example,

$$R_3GeGeR_3$$
$$R_3GeGe(R)_2Ge(R)_2GeR_3$$
$$R_3GeGe(R)_2Ge(R)_2Ge(R)_2GeR_3$$

and mixed Ge—Si and Ge—Sn compounds:

$$[R_3Ge]_3SiX, \quad [R_3Ge]_4Si, \quad R_3GeSnR_3$$

The germanium-carbon bonds are considerably more stable towards acids and halogens than the carbon-tin bonds but are inferior in strength to carbon-silicon bonds.

The principal routes for synthesis of organogermanium compounds are the following: the action of a Grignard reagent and other organometallic compounds on germanium tetrachloride and the addition to olefins of organic and inorganic derivatives of germanium, which contain a germanium-hydrogen bond, say, $HGeCl_3$. Just as in the case of silicon analogues, this addition formally occurs in contradiction to Markovnikov's rule. An example is

$$CH_3-CH=CH_2+HGeCl_3 \longrightarrow CH_3-CH_2-CH_2GeCl_3$$

Since the heterolysis of the H—Ge bond takes place in such a way that the hydrogen is split off as a hydride ion, the addition virtually proceeds according to Markovnikov's rule.

S. P. Kolesnikov and O. M. Nefedov have established that the π-systems of naphthalene and anisole (but not benzene and toluene) also add $HGeCl_3$. In the case of anisole, the addition occurs across

all the three bonds and a trigermanium derivative of methoxycyclohexane, $CH_3OC_6H_8(GeCl_3)_3$, is formed.

I. F. Lutsenko and I. Yu. Baukov have found that the exchange reaction

$$(CH_3)_3GeBr + (C_3H_7)_3SnCH_2-\overset{\overset{O}{\|}}{C}-CH_3 \xrightarrow[-(C_3H_7)_3SnBr]{}$$

$$\rightarrow (CH_3)_3GeCH_2\overset{\overset{O}{\|}}{C}-CH_3 + (CH_3)_3Ge-O-\overset{\overset{CH_3}{|}}{C}=CH_2$$

leads to the formation of a tautomeric mixture of the keto and enol forms in the following proportions:

$$(CH_3)_3GeCH_2-\overset{\overset{O}{\|}}{C}-CH_3 \rightleftarrows (CH_3)_3Ge-O-\overset{\overset{CH_3}{|}}{C}=CH_2$$

(96%) (4%)

This is so far the only example of metallotropic keto-enol tautomerism.

The same authors have observed only an irreversible rearrangement for an analogous silicon derivative of the keto form:

$$R_3SiCH_2-\overset{\overset{O}{\|}}{C}-CH_3 \xrightarrow{\text{heat}} R_3Si-O-\overset{\overset{CH_3}{|}}{C}=CH_2$$

Organometallic Compounds of Tin and Lead. Organotin and organolead compounds result from the reaction of alkyl (and aryl) halides with alloys of these metals with sodium (B. Bartocha, M. Y. Gray)

$$4C_2H_5Cl + 4PbNa \rightarrow (C_2H_5)_4Pb + 4NaCl + 3Pb$$

or from the reaction of a Grignard reagent with the chlorides of these metals (Pfeiffer):

$$4RMgCl + SnCl_4 \rightarrow R_4Sn + 4MgCl_2$$
$$4RMgCl + 2PbCl_2 \rightarrow R_4Pb + Pb + 4MgCl_2$$

Apart from R_4Sn and R_4Pb, there also exist the whole series of less alkylated derivatives:

$RSnCl_3$	R_2SnCl_2	R_3SnCl	R_4Sn
$RPbCl_3$	R_2PbCl_2	R_3PbCl	R_4Pb

The action of $SnCl_4$ and, accordingly, $Pb(OCOCH_3)_4$ on the right-hand members of the series can yield the left-hand members. By reacting hydrogen chloride with R_4M it is also possible to eliminate radicals, one after another, replacing them by halogen. The left-hand members of the series can be reacted with a Grignard reagent

to prepare the right-hand ones, including mixed products. The thus obtained compounds, $SnRR'R''R'''$ have been resolved into the antipodes by Pope.

The alkylation of sodium stannite by an alkyl iodide may yield (R. Meyer) the salt of alkylstannonic acid (the hydrolysis product of $RSnCl_3$):

$$RI + \overset{II}{Sn}(ONa)_2 \longrightarrow R\overset{IV}{Sn}\begin{matrix} ONa \\ \diagdown\!\!\diagup \\ O \end{matrix} + NaI$$

As established by Kraus, R_3SnCl in liquid ammonia when reacted with sodium is converted into R_3SnNa. Under the same conditions R_2SnCl_2 undergoes conversions represented by the following scheme:

$$R_2SnCl_2 + 2Na \longrightarrow R_2Sn + 2NaCl$$

$$2R_2Sn + 2Na \longrightarrow \begin{matrix} R & R \\ | & | \\ NaSn-Sn & Na \\ | & | \\ R & R \end{matrix} \xrightarrow{+2Na} 2R_2SnNa_2$$

When R_3SnNa and R_2SnNa_2 are decomposed in ammoniacal solution by an ammonium salt, R_3SnH and R_2SnH_2 are respectively obtained. They can be prepared, just as $RSnH_3$, by the reduction of R_3SnCl, R_2SnCl_2 and $RSnCl_3$ by means of R_2AlH. These organotin hydrides are capable of adding on (formally, in contradiction to Markovnikov's rule) across double and triple bonds (Van-Kerk). The addition reaction is initiated by free radicals (e.g., those generated from isobutyroazodinitrile) and may also proceed as a telomerization reaction. In this way, olefinic organotin compounds are prepared from acetylenes:

$$R_3SnH + R'C{\equiv}CR' \longrightarrow \begin{matrix} R' & & H \\ \diagdown & & \diagup \\ & C=C & \\ \diagup & & \diagdown \\ R_3Sn & & R' \end{matrix}$$

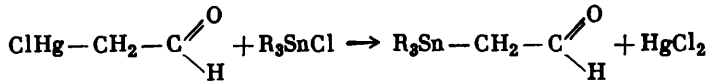
The functionally substituted organotin compounds of alkanes or cycloalkanes are formed from functionally substituted olefins, say, from unsaturated acids:

$$CH_2=\underset{\displaystyle H_3C}{\overset{|}{C}}-\underset{\displaystyle O}{\overset{\|}{C}}-OCH_3 + (C_2H_5)_2SnH_2 \longrightarrow (C_2H_5)_2SnH-CH_2-\underset{\displaystyle CH_3}{\overset{|}{CH}}-\underset{\displaystyle O}{\overset{\|}{C}}-OCH_3$$

The other methods of preparation of organotin compounds of the aliphatic series with functional substituents have been worked out by I. F. Lutsenko. The vinyl ethers and esters have proved to be capable of adding organotin alkoxides:

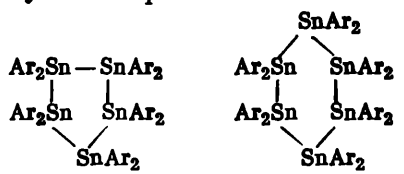
$$CH_2=CH-OC_4H_9 + R_3SnOCH_3 \longrightarrow R_3Sn-CH_2-CH\begin{matrix} OC_4H_9 \\ \diagdown\!\!\diagup \\ OCH_3 \end{matrix}$$

The exchange reaction of the α-mercury derivatives of carbonyl compounds with organotin halides can be used to readily synthesize the corresponding tin derivatives of carbonyl compounds:

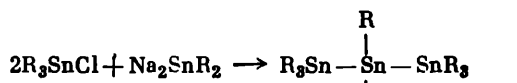


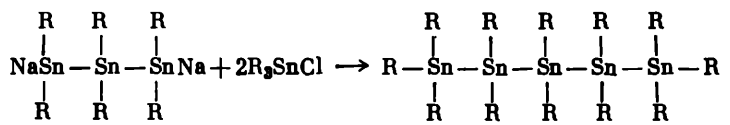
Aromatic organotin compounds with functional substituents can be prepared, according to A. N. Nesmeyanov and K. A. Kocheshkov, by the action of stannous chloride on aromatic organomercury compounds:

When R_3SnCl interacts with R_3SnNa, the product formed is $R_3Sn—SnR_3$ (it is interesting that, in contrast to $Ar_3C—CAr_3$, their tin analogues do not dissociate into free radicals). Longer chains of tin atoms, which are invariably unstable, are formed by the reduction of R_2SnCl_2 by less energetic agents than R_2AlH. From Ar_2SnCl_2 there are obtained cyclic compounds:



By combining sodium derivatives of organotin compounds with their chlorides it is possible to synthesize linear chains of 3-5 tin atoms:





The sodium derivatives R_2SnNa_2 and R_3SnNa can be utilized for alkylation at the tin atom, for example, for the preparation of compounds with a functional group in the chain:

Some of the organotin compounds, in particular, those of the type R_3SnX (where X = anion) have been found to be very potent fungicides and means for combating the fungus disease of plants and

animals. Aliphatic organotin compounds are used as stabilizers of plastics.

Lead, too, is known to have the following types of compounds: R_2Pb, R_3PbPbR_3, R_3PbNa (see also page 11).

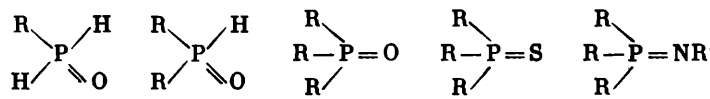
Tetraethyllead is used in large quantities as an antiknock agent in motor fuels (gasolines) for internal-combustion engines, which increase the quality of fuels (its action was discovered in 1922 by Midgley). A disadvantage of ethyl gasolines is their high toxicity.

12.6. Group V of the Periodic System

Organophosphorus Compounds. Two types of phosphorus-containing organic compounds are distinguished: (1) organophosphorus compounds proper, i.e., compounds whose molecules contain phosphorus linked directly to carbon; (2) various derivatives of inorganic phosphorus acids—esters, thioesters, amides, etc.; in these compounds, phosphorus is attached to carbon via oxygen, sulphur, nitrogen. Compounds of this type are widely distributed in nature. They include certain important enzymes and coenzymes, energy-carriers, such as adenosine triphosphate (see Volume III, page 423) and, finally, the nucleic acids of cells, which will be considered in Chapter 24. Organophosphorus compounds proper do not occur in nature*; they all have been obtained synthetically.

Like ammonia, phosphine, PH_3, is the parent compound of a number of organic derivatives—**phosphines.** According as how many hydrogen atoms are replaced by organic residues in phosphine, we speak of primary (RPH_2), secondary (R_2PH), or tertiary (R_3P) phosphine.

In contrast to the amines, phosphines are readily oxidized and enter into the various addition reactions. This gives rise to the following series of phosphine oxides, phosphine sulphides, and phosphine imines:



The alkylated derivatives of phosphines are **quaternary phosphonium salts,** $R_4P^+X^-$, which are analogous to quaternary ammonium salts.

The action of very strong bases (CH_3Li) on quaternary phosphonium salts containing at least one CHR group adjacent to phosphorus

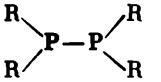
* The only exception is β-aminoethylphosphonic acid, $NH_2CH_2CH_2PO(OH)_2$, which is found in certain microorganisms, sea anemone, and also in *Rumen protozoon.*

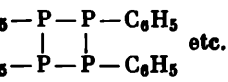
results in the formation of **methylenephosphines**, or **methylenephosphoranes**, which are sometimes called the **ylides** of phosphorus:

$$[(C_6H_5)_3\overset{+}{P}-CH_3]Cl^- \xrightarrow[-HCl]{} (C_6H_5)_3P=CH_2$$

Organophosphorus chemistry is characterized by the formation of halogen derivatives of the corresponding phosphines, $RPCl_2$ and R_2PCl. They may be regarded as the derivatives of phosphorus trichloride (and, in general, trihalide), PCl_3, in which the chlorine (halogen) atoms are replaced by organic radicals. But they may also be looked upon as phosphines in which the hydrogen atoms are replaced by chlorine atoms.

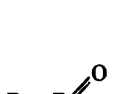
There are more complex derivatives of phosphorus, such as





etc.

Some phosphorus analogues of nitro compounds are known to exist, but, unlike nitrogen compounds, they are polymeric and their formula is II and not I:



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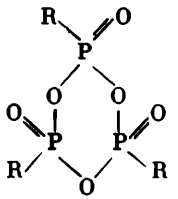
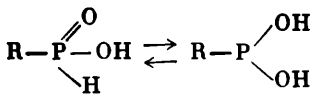
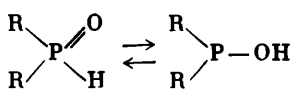


II

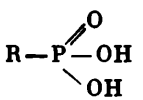
Generally, these compounds are not typical for organophosphorus chemistry. However, their hydrated forms, i.e., the organophosphorus acids of tri- and pentavalent phosphorus, constitute an important class of organophosphorus compounds. These include the acids:



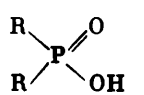
Phosphonous acids; salts and esters are phosphonites



Phosphinous acids; salts and esters are phosphinites



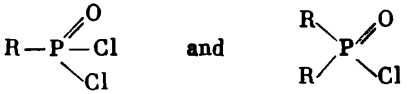
Phosphonic acids; salts and esters are phosphonates



Phosphinic acids; salts and esters are phosphinates

The various derivatives are known to exist for these acids: anhydrides, esters, amides, thio derivatives, etc. The above-mentioned

alkyl (aryl) dichlorophosphines, $RPCl_2$, may be regarded as the acid chlorides of phosphonous acids. Accordingly, the following acid chlorides are characteristic of phosphonic and phosphinic acids:



Finally, the replacement of oxygen by two halogen (chlorine) atoms in oxides of tertiary phosphines gives rise to the corresponding tertiary dihalophosphoranes, R_3PCl_2. These are derivatives of phosphorus pentachloride, in which all the chlorine atoms can be successively displaced by organic radicals:

$$RPCl_4 \qquad R_2PCl_3 \qquad R_3PCl_2 \qquad R_4PCl \qquad Ar_5P$$

All these compounds are known to exist and have been studied well, and some of them play an important part as intermediates in the synthesis of organophosphorus compounds.

Although phosphorus is the nearest neighbour of nitrogen in Group V of the periodic table and many types of organic compounds formed by both elements are formally equivalent, there are nevertheless many striking differences in their properties and structures. This is accounted for by differences in the configurations of the electron shells of nitrogen and phosphorus atoms since nitrogen is a second-period element and phosphorus is a third-period element. The electron shell of the nitrogen atom is characterized by the *L* level being filled, the three 2*p* orbitals each having one electron. Therefore, nitrogen has a covalency of 3 (sp^2 hybridization) and of 4 (sp^3 hybridization).

K	*L*								
$1s^2$	$2s^2$	$2p$	$2p$	$2p$					

The outer electron shell of the phosphorus atom contains only a partially filled *M* level:

K	*L*				*M*				
$1s^2$	$2s^2$	$2p^2$	$2p^2$	$2p^2$	$3s^2$	$3p$	$3p$	$3p$	

and, apart from the valence states p^3 (trivalent phosphorus) and sp^3 (phosphonium phosphorus), phosphorus is capable of being in the sp^3d valence state (pentacovalent phosphorus) and even in the sp^3d^2 valence state (hexacovalent phosphorus, say, in the anion PF_6^-). This ability to exhibit higher covalencies is very characteristic of phosphorus. Owing to this ability, phosphorus (and also arsenic, antimony, and bismuth, as we shall see later) can form compounds

such as, for example, $(C_6H_5)_5P$ (the symmetry of the phosphorus bonds is a trigonal bipyramid), which are impossible for nitrogen. This also accounts for the predominance of the *ortho*-forms of oxyacids of phosphorus and of *meta*-forms of those of nitrogen. Thus, there is only one acid known for nitrogen, namely, nitric acid, HNO_3, which belongs to the *meta*-series, just like metaphosphoric acid, HPO_3. But for phosphorus the most stable is orthophosphoric acid, H_3PO_4, which is impossible for nitrogen. Derivatives of fully hydrated phosphoric acid are also known, say, $(C_6H_5O)_5P$. While nitro compounds, RNO_2, are characteristic of the nitrogen chemistry, the chemistry of phosphorus is known to have the corresponding hydrated forms: phosphonic acids, $RP(O)(OH)_2$, their esters, $RP(O)(OR)_2$, and even orthoesters, $RP(OR)_4$.

In the chemistry of nitrogen-containing organic compounds, the most stable forms are amines having only very weak reducing properties. The oxides of tertiary amines, $R_3N \rightarrow O$ and even nitro compounds are substances with pronounced oxidizing properties (oxides of tertiary amines, for example, evolve iodine from an acidified solution of potassium iodide). In the chemistry of organophosphorus compounds, the most stable are derivatives of phosphorus in the higher valence states: phosphines are strong reducing agents (the lower phosphines are spontaneously inflammable in air), and the oxides of tertiary phosphines, and phosphonic and phosphinic acids have no oxidizing properties at all. On the other hand, there are certain nitrogen functions, such as azo compounds, R—N=N—R, which do not exist in the phosphorus chemistry. All attempts to synthesize compounds of this kind have resulted only in the formation of dimers:

$$\begin{array}{c} R-P-P-R \\ \quad | \quad | \\ R-P-P-R \end{array}$$

The basis of the chemistry of organophosphorus compounds was laid by the works of Michaelis and A. E. Arbuzov.

Phosphines. Primary and secondary phosphines, unlike amines, are difficultly available substances. They can be prepared by one of the following reactions:

(1) alkylation of metal phosphides

$$PH_2Na + RI \longrightarrow RPH_2 + NaI$$

or

$$RPHLi + R'Br \longrightarrow RR'PH + LiBr$$

(2) reduction of chlorophosphines by lithium aluminium hydride or trichlorosilane (silicochloroform), $SiHCl_3$:

$$RPCl_2 \xrightarrow{H} RPH_2$$

(3) addition of a phosphine to unsaturated compounds by the Kharasch method (initiation with peroxides):

$$C_6H_{13}CH=CH_2+PH_3 \longrightarrow C_6H_{13}-\underset{\displaystyle CH_3}{CH}-PH_2$$

Tertiary phosphines are readily synthesized by the action of a Grignard reagent or organolithium compounds on phosphorus trichloride:

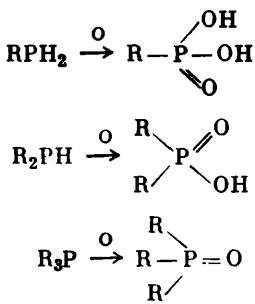
$$3RMgBr+PCl_3 \longrightarrow R_3P+3MgBrCl$$

Furthermore, they can be prepared by the reduction of oxides of tertiary phosphines with trichlorosilane:

$$(C_6H_5)_3PO \xrightarrow{SiHCl_3} (C_6H_5)_3P$$

In rare cases, tertiary phosphines are made by alkylation of primary or secondary phosphines.

Primary and secondary phosphines when oxidized under mild conditions are converted into the corresponding phosphonic and phosphinic acids, while tertiary phosphines are converted into oxides:



The lower aliphatic phosphines are readily oxidizable compounds. **Methylphosphine**, CH_3PH_2, **dimethylphosphine**, $(CH_3)_2PH$, and **trimethylphosphine**, $(CH_3)_3P$, are spontaneously flammable in air.

The phosphines are but very weak bases, and their salts are easily hydrolysed by water. They readily form complex compounds with salts of heavy metals, and are also capable of displacing CO from metal carbonyls:

$$Ni(CO)_4+(C_6H_5)_3P \longrightarrow (C_6H_5)_3P\cdots Ni(CO)_3+CO$$

Certain complexes of triphenylphosphine with salts of heavy metals are used as catalysts for the Reppe syntheses and analogous reactions (see Volume I, page 356).

When tertiary phosphines are alkylated, salts of quaternary phosphonium bases are formed; for example:

$$(CH_3)_3P + CH_3I \longrightarrow (CH_3)_4P^+ I^-$$

$$(C_6H_5)_3P + CH_3I \longrightarrow (C_6H_5)_3\overset{+}{P}CH_3\ I^-$$

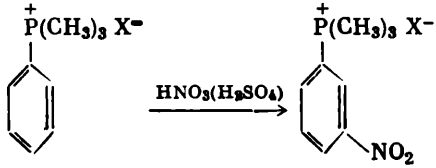
These are salts of strong bases, similar to ammonium and sulphonium bases.

Various phosphonium salts are known, which contain other functional groups in hydrocarbon radicals, say, hydroxy groups. For example, tetramethylolphosphonium chloride is made by the condensation of phosphine with formaldehyde in the presence of hydrochloric acid:

$$PH_3 + 4CH_2O + HCl \longrightarrow (HOCH_2)_4P^+ Cl^-$$

It is used for impregnation of fabrics followed by the treatment with substances which form polymers with its hydroxyl groups. Such an impregnation renders fabrics fire-proof.

The phosphonium group is a strong *meta*-director in substitution reactions in the benzene ring. For instance, the nitration of trimethylphenylphosphonium chloride gives quantitative yields of the *meta*-substituted compound:



Quaternary phosphonium salts containing at least one alpha-hydrogen lose a molecule of HX under the action of rather strong bases, forming alkylidenephosphoranes (phosphinemethylenes) (Wittig):

$$(C_6H_5)_3\overset{+}{P}-CHR_2X^- + C_6H_5Li \longrightarrow (C_6H_5)_3P=CR_2 + C_6H_6 + LiX$$

The electron-density distribution in alkylidenephosphoranes is intermediate between the "ylene" and "ylide" formulas:

$$\underset{\text{Phosphorylene}}{R_3P=CR'R''} \longleftrightarrow \underset{\text{Phosphorylide}}{R_3\overset{+}{P}-\overset{-}{C}R'R''}$$

These are very reactive compounds, especially if R′ and R″ are alkyl or hydrogen; they are rapidly oxidized in air and hydrolysed. Considerably more stable are alkylidenephosphoranes with electron-attracting substituents. For example,

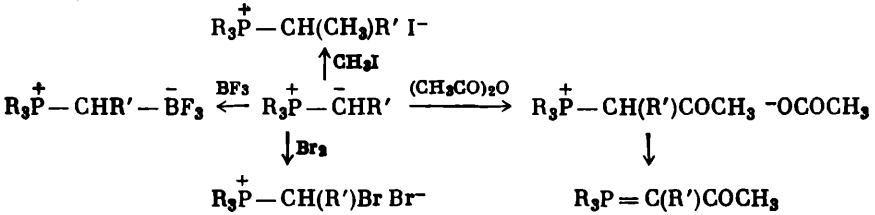
$$R_3P=CH-\underset{\underset{O}{\|}}{C}-R \longleftrightarrow R_3\overset{+}{P}-CH=\underset{\underset{O^-}{|}}{C}-R$$

According to the stability of acylmethylenetriphenylphosphoranes, their protonated forms, i.e., the corresponding phosphonium salts, are relatively strong acids. Thus, triphenylphenacylphosphonium bromide I is an acid comparable in strength to acetic acid, and triphenyldibenzoylmethylphosphonium bromide II is a stronger acid than oxalic acid (M. I. Kabachnik, T. A. Mastryukova):

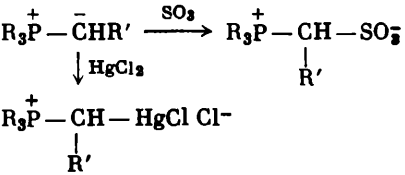
$$(C_6H_5)_3\overset{+}{P}CH_2COC_6H_5\ Br^- \qquad (C_6H_5)_3\overset{+}{P}CH(COC_6H_5)_2\ Br^-$$

I (pK_a 6.3 in 50-percent alcohol) II (pK_a 2.6 in 50-percent alcohol)

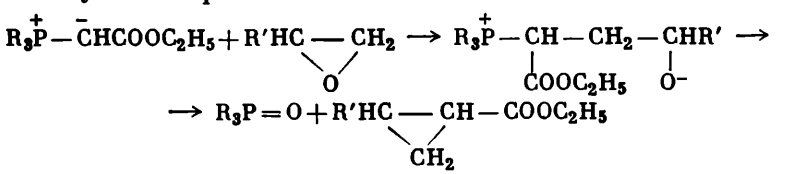
Alkylidenephosphoranes are strong nucleophilic reagents and, as such, react with halogens, alkyl and acyl halides, etc. (Bestmann, Märkl):



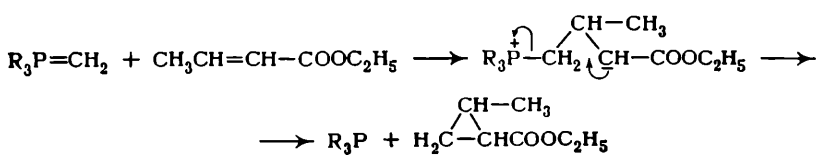
Stable phosphorylides (with electron-attracting groups) smoothly add sulphur trioxide and mercuric chloride (N. A. Nesmeyanov, O. A. Reutov):



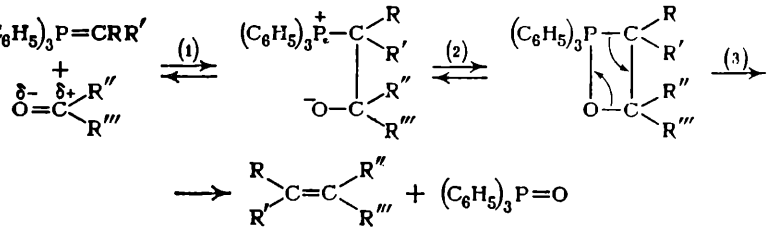
Certain phosphorylides react with α-oxides to form three-membered alicyclic compounds:



Three-membered rings are also produced by the interaction of ylides with compounds containing activated double bonds:



The most important reaction of phosphinemethylenes is the **Wittig reaction**—the interaction of phosphinemethylenes with carbonyl compounds (aldehydes and ketones). The products obtained by this reaction are olefins and triphenylphosphine oxide (see Volume I, page 335). The reaction enables a double bond to be introduced simultaneously with the building-up of the carbon chain. It proceeds under mild conditions with good yields, and the position of the double bond causes no doubt. At present the Wittig reaction is widely employed in fine organic synthesis and especially in the synthesis of natural compounds. The mechanism of this reaction consists in the following:



The first stage is the nucleophilic addition of the Wittig reagent (phosphinemethylene) across the C=O double bond. An intermediate heterocyclic compound is then probably formed, which decomposes irreversibly into a phosphine oxide and an olefin.

Chlorophosphines. Chlorophosphines are mostly liquids with a sharp penetrating smell, which fume in air. They are prepared by several methods:

(1) from organomercury compounds and phosphorus trichloride under rather drastic conditions:

$$(C_2H_5)_2Hg + PCl_3 \longrightarrow C_2H_5PCl_2 + C_2H_5HgCl$$

(2) by the action of tetraalkyllead on phosphorus trichloride:

$$(C_2H_5)_4Pb + PCl_3 \longrightarrow C_2H_5PCl_2 + (C_2H_5)_3PbCl$$

(3) by the direct alkylation of red phosphorus by alkyl halides in the presence of copper (B. M. Gladshtein, L. Z. Soborovsky):

$$3CH_3Cl + 2P \xrightarrow{Cu} CH_3PCl_2 + (CH_3)_2PCl$$

(4) by the reduction of complex compounds of an alkyl halide, aluminium chloride and phosphorus trichloride:

$$[RPCl_3]^+[AlCl_4]^- \xrightarrow{Mg} RPCl_2 + AlCl_3 + MgCl_2$$

(5) by the reduction of compounds of the type $RPCl_4$, say, with methyl dichlorophosphite:

$$RPCl_4 + CH_3OPCl_2 \longrightarrow RPCl_2 + CH_3Cl + POCl_3$$

Aromatic chlorophosphines are produced by the Friedel-Crafts reaction from hydrocarbons and phosphorus trichloride under the action of aluminium chloride (A. Michaelis)

$$C_6H_6 + PCl_3 \xrightarrow{AlCl_3} C_6H_5PCl_2 + HCl$$

or by the direct phosphorylation of benzene at a high temperature (A. Michaelis, A. E. Arbuzov):

$$C_6H_6 + PCl_3 \longrightarrow C_6H_5PCl_2 + HCl$$

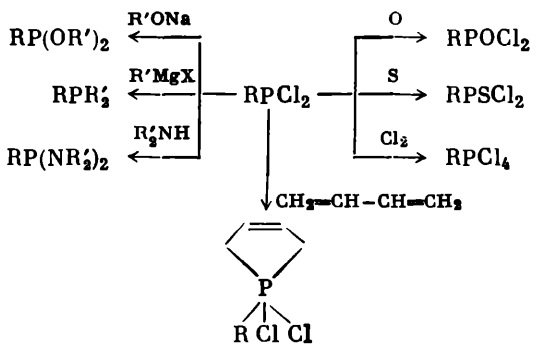
They can also be synthesized from chlorobenzene, phosphorus and phosphorus trichloride:

$$3C_6H_5Cl + 2P + PCl_3 \longrightarrow 3C_6H_5PCl_2$$

Secondary aromatic chlorophosphines are prepared by the disproportionation of primary aromatic chlorophosphines under the catalytic action of aluminium chloride (M. I. Kabachnik, T. Ya. Medved):

$$2C_6H_5PCl_2 \xrightarrow{AlCl_3} (C_6H_5)_2PCl + PCl_3$$

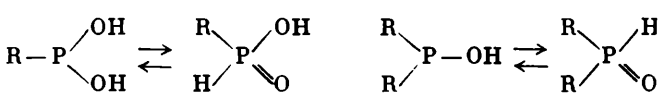
Chlorophosphines, especially aromatic ones, are important intermediates in the synthesis of other types of organophosphorus compounds. For example,



Phosphonous and Phosphinous Acids. These acids are formed on careful hydrolysis of the corresponding chlorophosphines:

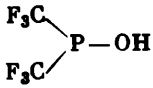
$$RPCl_2 + 2H_2O \longrightarrow RPO_2H_2 + 2HCl$$
$$R_2PCl + H_2O \longrightarrow R_2POH + HCl$$

They are tautomeric compounds (diad tautomerism):



Phosphonous acid Phosphinous acid

For the acids with alkyl or aryl groups attached to phosphorus the equilibrium is considerably shifted to the side of tautomers with formally pentavalent phosphorus. However, the introduction of strongly electronegative substituents, such as the CF_3 group, shifts the equilibrium to the opposite side, and, for example, bis-(trifluoromethyl)-phosphinous acid corresponds to the hydroxyl form



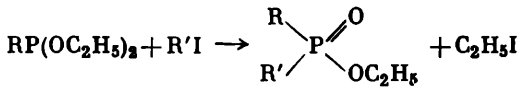
Free phosphonous and phosphinous acids are less important than their esters and other derivatives. The esters of these acids—**phosphonites** and **phosphinites**—are obtained by the reaction of chlorophosphines with alkoxides or alcohols in the presence of tertiary amines:

$$RPCl_2 + 2NaOC_2H_5 \longrightarrow RP(OC_2H_5)_2 + 2NaCl$$

$$R_2PCl + C_4H_9OH + (C_2H_5)_3N \longrightarrow R_2POC_4H_9 + (C_2H_5)_3\overset{+}{N}H\,Cl^-$$

They are also prepared from chlorophosphites, $(R'O)_2PCl$ or $R'OPCl_2$, by the reaction with organomagnesium compounds at a low temperature (M. I. Kabachnik, E. N. Tsvetkov).

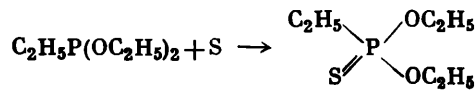
A characteristic property of these esters is their ability to rearrange under the action of alkylhalides (the Arbuzov rearrangement; see below). Phosphonites in this reaction give the esters of dialkylphosphinic acids



and phosphinites yield the corresponding oxides of tertiary phosphines:

$$R_2POC_2H_5 + RI \longrightarrow R_3P{=}O + C_2H_5I$$

These esters readily add sulphur with the formation of the corresponding esters of thiophosphonic (and thiophosphinic) acids:

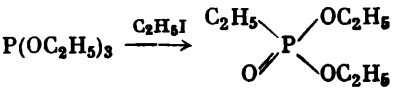


Phosphonic and Phosphinic Acids. These are evidently the most important classes of organophosphorus compounds because of their great number and practical significance. The principal methods of preparation of these compounds are the following.

1. The rearrangement of esters of phosphorous acid (phosphites)* or alkylphosphonous acids (phosphonites) under the action of alkyl

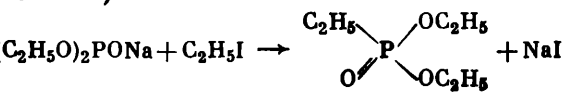
* The phosphites themselves are prepared, according to Milobendzki, by the interaction of PCl_3 and an alcohol (even a primary one) in the presence of R_3N.

halides (the Arbuzov rearrangement):



It is natural that in the case of esters of phosphorous acid the rearrangement gives esters of alkylphosphonic acids, and when esters of alkylphosphonous acids undergo the rearrangement, the corresponding esters of dialkylphosphinic acids are formed. When the esters are saponified, the acids themselves are readily liberated.

2. The alkylation of sodium salts of dialkyl phosphites (the Michaelis-Becker reaction):



3. The alkylation of phosphorus trichloride with alkyl halides in the presence of aluminium chloride:

$$RCl + PCl_3 + AlCl_3 \longrightarrow [RPCl_3]^+ [AlCl_4]^-$$

The initially formed complexes are hydrolysed by water and form an alkylphosphonic acid:

$$[RPCl_3]^+ [AlCl_4]^- + 3H_2O \longrightarrow RPO(OH)_2 + 4HCl + AlCl_3$$

4. The hydrolysis of acid chlorides of the types $RPOCl_2$ and R_2POCl:

$$RPOCl_2 + 2H_2O \longrightarrow RPO(OH)_2 + 2HCl$$

5. The starting materials commonly used for the preparation of aromatic phosphonic acids are aryldichlorophosphines:

$$C_6H_5PCl_2 + Cl_2 \longrightarrow C_6H_5PCl_4 \xrightarrow{3H_2O} C_6H_5PO(OH)_2 + 4HCl$$

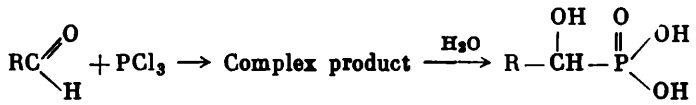
6. A specific reaction for the synthesis of aromatic phosphonic acids is the reaction of aryldiazonium borofluorides with phosphorus trichloride in the presence of copper (the Freedman-Doak method):

$$[ArN_2]^+ [BF_4]^- + PCl_3 \longrightarrow [ArPCl_3]^+ [BF_4]^- + N_2$$
$$[ArPCl_3]^+ [BF_4]^- + 3H_2O \longrightarrow ArPO(OH)_2 + 3HCl + HBF_4$$

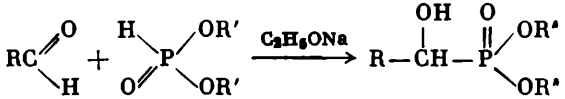
There are many specific methods of synthesis of phosphonic and phosphinic acids containing various functional groups in the alkyl radical.

Hydroxyalkylphosphonic acids are prepared by the reaction of phosphorus trichloride with aldehydes, usually in a medium of glacial acetic acid. In this reaction, an addition product of complex composition is first formed, which on hydrolysis is converted into a

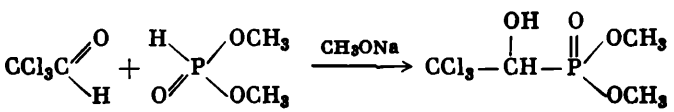
hydroxyalkylphosphonic acid (the Fossek-Page-Conant reaction):



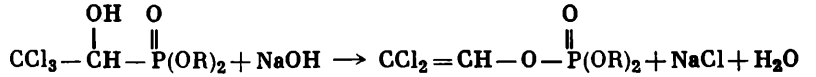
The esters of hydroxyalkylphosphonic acids are easily produced as a result of the addition of dialkyl phosphites to aldehydes and ketones in the presence of alkoxides as catalysts (V. S. Abramov):



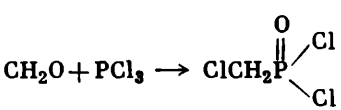
In this way, a widely used insecticide, **chlorophos**, is synthesized from chloral and dimethyl phosphite:



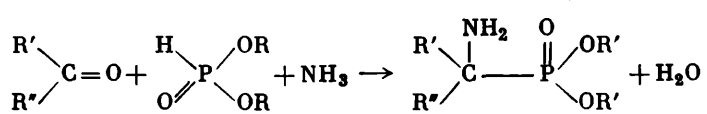
α-Hydroxyalkylphosphonic esters readily undergo rearrangement under the action of alkali into the unsaturated esters of phosphoric acid (Schrader):



When aldehydes are heated with phosphorus trichloride in sealed tubes or autoclaves up to 200-250°C, the acid chlorides of α-chloroalkylphosphonic acids are formed (M. I. Kabachnik, E. S. Shepeleva):

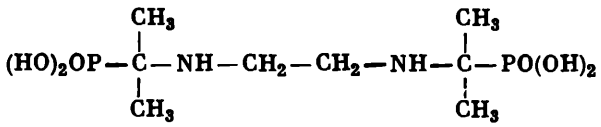


α-Aminoalkylphosphonic acids are made by the condensation of dialkyl phosphites, aldehydes (or ketones) and ammonia or amines (M. I. Kabachnik, T. Ya. Medved; E. K. Fields):



Aminophosphonic acids, like aminocarboxylic acids, possess the ability to form inner-complex compounds with salts of heavy metals. Particularly powerful complex-formers are polyaminopolyphospho-

nic acids of the following type (M. I. Kabachnik, N. M. Dyatlova):



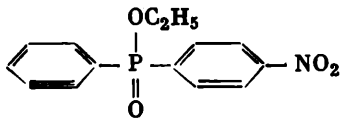
Phosphicine

Phosphonic acids usually crystallize well; they are relatively strong acids ($K_a = 10^{-2}$-10^{-3} in aqueous solution). When the salts are esterified or alkylated, only acid esters of these acids can mainly be prepared. The neutral esters are made via the acid chlorides according to the scheme:

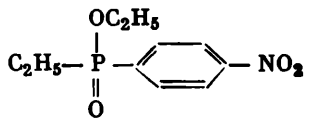
$$RPO(OH)_2 + 2PCl_5 \longrightarrow RPOCl_2 + 2POCl_3 + 2HCl$$

$$RPOCl_2 + 2R'OH + 2(C_2H_5)_3N \longrightarrow \underset{\displaystyle O \quad OR'}{\overset{\displaystyle R \quad OR'}{P}} + 2(C_2H_5)_3\overset{+}{N}H\ Cl^-$$

The derivatives of phosphonic and phosphinic acids find application as insecticides in the warfare against pests. In addition to chlorophos described above, mention should be made of the EPN preparation widely used in foreign countries and its ethyl analog—the drug **armine** which is employed for the treatment of glaucoma.

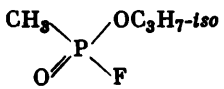


EPN



Armine

The derivatives of methylphosphonic acid include the chemical warfare agent Sarin (one of the so-called nerve gases):

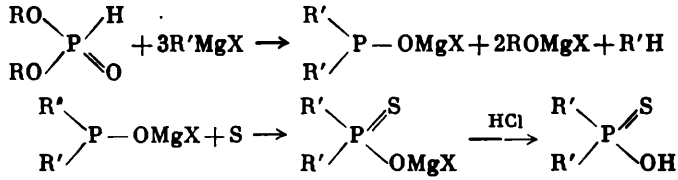


If an oxygen in phosphonic or phosphinic acids is replaced by sulphur, **thiophosphonic** and **thiophosphinic** acids will result, respectively:

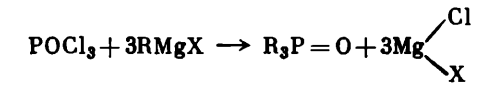
The derivatives of thiophosphonic acids are commonly prepared by adding sulphur to the corresponding compounds of trivalent phosphorus:

$$RPCl_2 + S \longrightarrow \underset{\displaystyle S \quad Cl}{\overset{\displaystyle R \quad Cl}{P}}$$

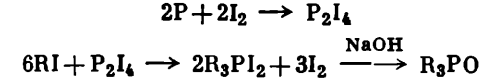
The best method of preparing thiophosphinic acids is by the action of organomagnesium compounds on dialkyl phosphites followed by the addition of sulphur (M. I. Kabachnik, T. A. Mastryukova):



Oxides of Tertiary Phosphines. These substances are usually made by the interaction between Grignard reagents and phosphorus oxychloride:

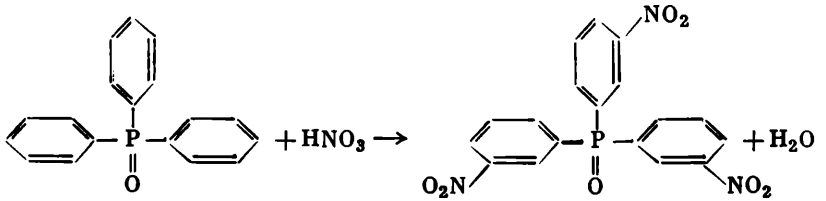


They can also be prepared by the oxidation of tertiary phosphines or by the Arbuzov rearrangement of esters of dialkylphosphinous acids. An interesting method has recently been devised for the synthesis of oxides of tertiary phosphines by the alkylation of red phosphorus with alkyl iodides in the presence of catalytic amounts of iodine (A. V. Kirsanov):



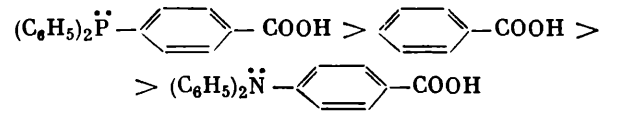
The oxides of tertiary phosphines are crystalline substances which are oxidized and reduced with difficulty. They possess weakly basic properties and readily form complexes with salts of metals. These oxides (e.g., trioctylphosphine oxide) are used for extraction of salts of uranium and other metals from solutions.

The phosphoryl group P=O is an electron-attracting *meta*-directing group. Thus, the nitration of triphenylphosphine oxide gives tri-*m*-nitrotriphenylphosphine oxide:



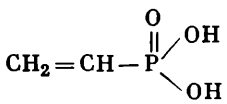
Somewhat unexpected are the electron-attracting ($-I$ and $-M$ effects) properties of groupings with trivalent phosphorus. The phosphorus atom in such groupings bears an unshared electron pair and might be expected to display electron-donating properties, like the

nitrogen in amino groups. Diphenylphosphinobenzoic acid, however, has proved to be stronger than benzoic acid, whereas diphenylaminobenzoic acid is weaker than benzoic acid:

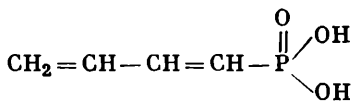


This phenomenon has been accounted for by the character of hybridization of the unshared electron pairs on phosphorus and nitrogen. Whereas the unshared electron pair on nitrogen (hybridization approaches sp^2) has a pronounced p-character, the unshared electron pair on phosphorus (hybridization approaches sp^3) is almost in a pure s-state. Accordingly, it cannot interact with the π-electrons of the ring (M. I. Kabachnik, E. N. Tsvetkov, D. A. Bochvar).

Apart from organophosphorus compounds with alkyl or aryl groups, phosphorus has been shown to form the corresponding unsaturated compounds, derivatives of ethylene and its homologues, acetylene, dienes, etc. Two examples are cited below:



Vinylphosphonic acid

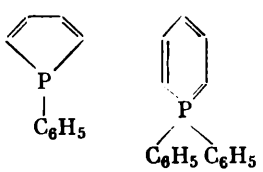


Butadienylphosphonic acid

The vinyl group linked to phosphorus readily add nucleophilic reagents in the β-position.

Organophosphorus unsaturated compounds are capable of polymerization and copolymerization with other unsaturated compounds. Polymers containing phosphonic and analogous groups are noncombustible and inflame difficultly.

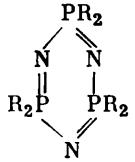
Organophosphorus analogues of nitrogen-containing heterocyclic systems of pyrrole and pyridine are known to exist:

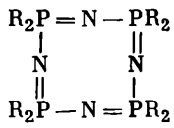


I II

but these compounds have no aromatic properties and are true dienes (they enter into diene synthesis and other reactions). This is ascribed to the difficulty of formation of an aromatic sextet with the participation of the $3p$- and $3s$-hybridized electrons on phosphorus in compound I (the formation of an aromatic sextet in compound II involves $3d$-electrons).

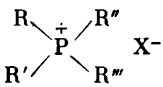
The stable heterocyclic systems of tri- and tetraphosphonitriles should also be mentioned here:

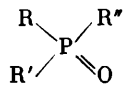




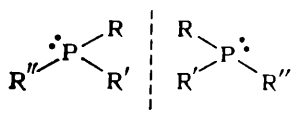
In contrast to triazines, the molecules of triphosphonitriles are not flat. Some of them undergo polymerization with ring-opening and formation of rubber-like polymers.

Stereochemistry of Non-Carbon Atoms of Tetrahedral Configuration. The tetraalkylphosphonium (ammonium, arsonium) cations and also oxides of tertiary phosphines have a structure similar to that of carbon compounds since the central atom is linked to four substituents:

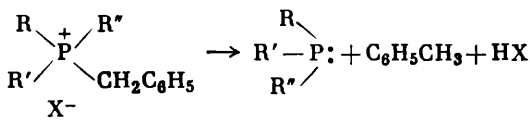




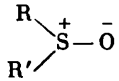
This is why unsymmetrical phosphonium salts should be expected to display optical stereoisomerism. Quaternary ammonium salts were first resolved into optical antipodes by Pope in 1899; the quaternary phosphonium salts and phosphine oxides containing phosphorus in the ring as a hetero-atom were resolved into antipodes by Meisenheimer in the twenties of this century. Ordinary quaternary phosphonium salts could only be resolved into optical antipodes in the sixties of this century by McEwen and Vander Werf. The most interesting discovery, however, was made by Horner in 1964; he obtained a number of optically active tertiary phosphines



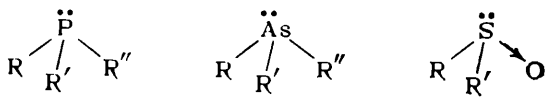
For this purpose he made use of the fact established by him that quaternary phosphonium salts containing benzyl at the phosphorus atom are smoothly reduced electrochemically (cathodic reduction) to tertiary phosphines:



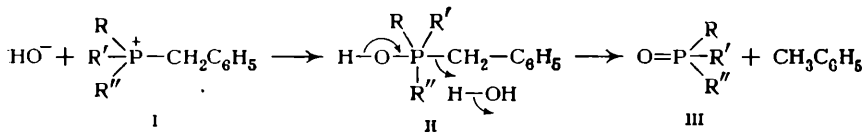
Thus, in tertiary phosphines the free electron pair on phosphorus retains its configuration and, in this sense, plays the role of a fourth radical. This fact distinguishes tertiary phosphines from tertiary amines. Such stereochemical relations were known earlier for sulphoxides that have a pyramid structure, the oxygen being linked to sulphur by a semipolar bond.



The preparation of the optically active compounds of tri- and tetracovalent phosphorus was followed by the isolation of the corresponding compounds of arsenic and sulphur, and the study of the stereochemistry of some of their reactions.



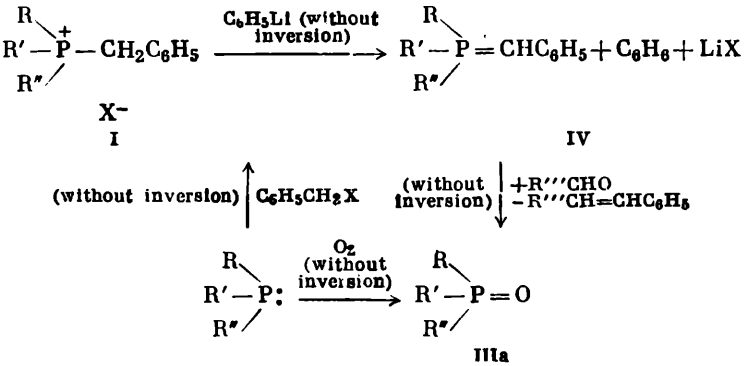
Of the phosphonium salts containing a benzyl group, there can be prepared phosphine oxide III either with retention or with inversion of configuration, depending on the method of synthesis. On alkali hydrolysis there takes place an inversion of configuration:



The intermediate compound II is formally similar to the transition state in a nucleophilic substitution at the unsaturated carbon atom (S_N2). The difference, however, is that, in contrast to carbon, phosphorus can accommodate 10 electrons in its outer shell by utilizing its empty 3*d* orbitals and form pentacovalent compounds; therefore the energy of compound II must lie at a minimum on the potential curve. The second stage of this reaction must involve a water molecule for the benzyl ion to be detached.

The action of phenyllithium on the same salt I results in the formation of a reactive ylide IV which reacts with an aldehyde by the Wittig reaction (page 71), forming an olefin and phosphine oxide

IIIa without change of configuration



since the asymmetric centre remains intact in the formation of the ylide, and the Wittig reaction proceeds through a cyclic intermediate which permits of no inversion.

When a tertiary phosphine is oxidized, the configuration does not change either; nor does it change when the tertiary phosphine is alkylated with an alkyl halide since the alkyl radical acquires a free electron pair which holds the configuration.

Organoarsenic Compounds. By reacting a Grignard reagent with arsenic trichloride it is possible to prepare a trialkylarsine, R_3As, and with other reagent ratios an alkyldichloroarsine, $RAsCl_2$, and a dialkylchloroarsine, R_2AsCl, are also obtained. The dry distillation of As_2O_3 with sodium acetate gave **cacodyl oxide*** (Bunsen):

$$4CH_3-\overset{\overset{O}{\|}}{C}-ONa + As_2O_3 \longrightarrow (CH_3)_2As-O-As(CH_3)_2 + Na_2CO_3 + 2CO_2$$

When cacodyl oxide is allowed to react with HCl, dimethylchloroarsine, $(CH_3)_2AsCl$, is formed.

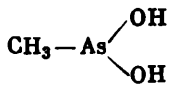
The energetic reduction of $RAsCl_2$ and R_2AsCl leads to the formation of an alkylarsine, $RAsH_2$, and a dialkylarsine, R_2AsH, which are very toxic and are readily oxidized by the air.

The action of alkyl iodides on an arsenite gives rise to **dialkylarsinic** or **alkylarsonic acids.** The reaction takes place with transfer of the reaction centre:

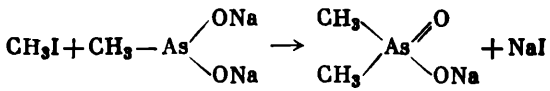
$$CH_3I + Na_3AsO_3 \longrightarrow \underset{\text{Arrhenal}}{CH_3As(O)(ONa)_2} + NaI$$

* The radical $(CH_3)_2As$ was named the cacodyl radical during the reign of the theory of radicals.

Methylarsonic acid can be reduced, say, by the action of SO_2 to methylarsenous acid



When its salt is methylated, the salt of dimethylarsenic acid is formed:



Alkyl halides add to trialkylarsines, forming tetraalkylarsonium salts:

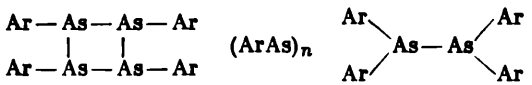
$$R_3As + RI \longrightarrow R_4As^+ I^-$$

The corresponding hydroxides $R_4As^+ OH^-$ are strong bases; their salts with strong acids are not noticeably hydrolysed by water.

Just like aliphatic organoarsenic compounds, aromatic compounds of the following structures are also known (Ar = aryl, X = halogen)

1. Compounds of As(III):

$ArAsH_2$, Ar_2AsH, Ar_3As; $ArAsX_2$, Ar_2AsX; $ArAs(OH)_2$, Ar_2AsOH



2. Compounds of As(V):

$ArAsX_4$, Ar_2AsX_3, Ar_3AsX_2, Ar_4AsX, Ar_5As;

$ArAsO(OH)_2$, $Ar_2AsO(OH)$, Ar_3AsO, $Ar_4\overset{+}{A}s\ OH^-$

The starting materials commonly used for the synthesis of organoarsenic compounds are triarylarsines or arylarsenic acids.

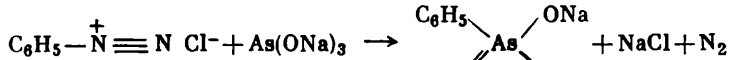
Triarylarsines can be obtained, according to Michaelis, by a modification of the Wurtz reaction, through the action of sodium on a mixture of arsenic trichloride and an aryl halide:

$$3C_6H_5Cl + 6Na + AsCl_3 \longrightarrow (C_6H_5)_3As + 6NaCl$$

or, more simply, by the action of a phenylmagnesium halide on arsenic trichloride (according to Pfeiffer):

$$3C_6H_5MgBr + AsCl_3 \longrightarrow (C_6H_5)_3As + 3MgClBr$$

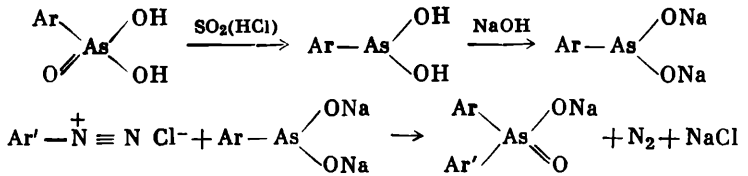
Arylarsenic acids can be obtained by the Bart method via diazo compounds:



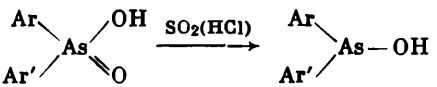
or by the direct arsenation. In the latter case the aromatic ring must be considerably activated to electrophilic substitution by the presence of NH_2, OH and similar substituents. An example is the preparation of arsanilic acid by the Béchamps method:

$$C_6H_5NH_2 + H_3AsO_4 \longrightarrow p\text{-}NH_2C_6H_4AsO(OH)_2 + H_2O$$

Diarylarsenic acid too can be made via diazo compounds if arylarsenic acid is reduced to arylarsenous acid, the latter being then reacted with a diazonium salt:



The reduction of diarylarsenic acid can yield diarylarsenous acid:



Arylarsenous acids are converted by the action of concentrated hydrochloric acid into aryl- or, accordingly, diarylchloroarsines:

$$ArAs(OH)_2 + 2HCl \longrightarrow ArAsCl_2 + 2H_2O$$
$$Ar_2AsOH + HCl \longrightarrow Ar_2AsCl + H_2O$$

which in their turn on reduction with zinc dust in acid medium give aryl- or diarylarsines:

$$ArAsCl_2 \xrightarrow{Zn(H^+)} ArAsH_2$$
$$Ar_2AsCl \xrightarrow{Zn(H^+)} Ar_2AsH$$

Aryl- and diarylarsines show no resemblance to the amines. They have no basic properties and are strong reducing agents.

The less energetic reduction of $ArAsCl_2$ (accordingly, Ar_2AsCl) in alkaline medium, say, with phosphorous acid, yields **arseno compounds** and **cacodyls**. Both types of compounds can also be prepared by the interaction of $ArAsH_2$ (or Ar_2AsH) with aryl- and diarylchloroarsines:

$$2ArAsH_2 + 2ArAsCl_2 \longrightarrow \underset{\text{Arsenobenzene}}{Ar{-}As{-}As{-}Ar \;\; Ar{-}As{-}As{-}Ar} + 2HCl$$

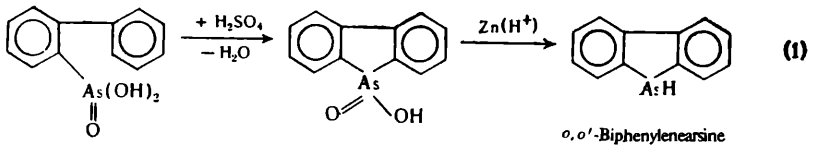
$$Ar_2AsH + Ar_2AsCl \longrightarrow \underset{\text{Phenylcacodyl}}{Ar_2As{-}AsAr_2} + HCl$$

When reacted with a halogen, arsenobenzene is converted into $ArAsCl_2$ and then into $ArAsCl_4$, and phenylcacodyl turns into Ar_2AsCl and further into Ar_2AsCl_3.

The compounds $ArAsCl_2$ and Ar_2AsCl can also be made as a result of a disproportionation reaction by prolonged heating of $AsCl_3$ with Ar_3As:

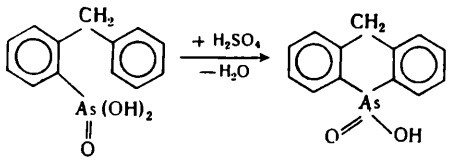
$$Ar_3As + AsCl_3 \longrightarrow ArAsCl_2 + Ar_2AsCl$$

The following reactions of intramolecular arsenation have been used to prepare heterocyclic compounds with arsenic as a heteroatom:



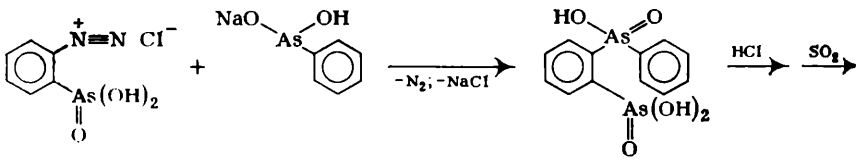
(1)

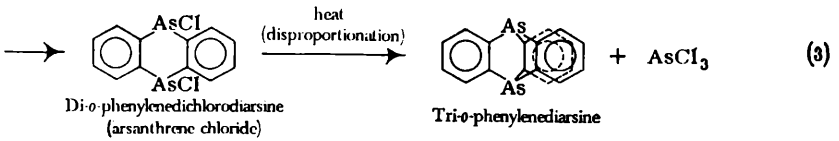
o,o'-Biphenylenearsine



(2)

Acridarsonic acid



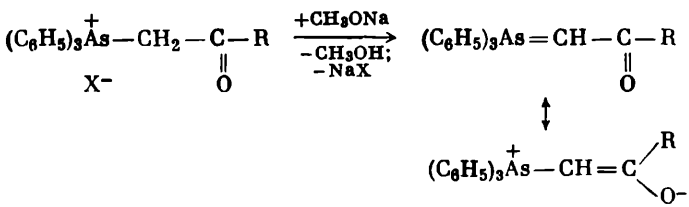


(3)

Di-o-phenylenedichlorodiarsine (arsanthrene chloride)

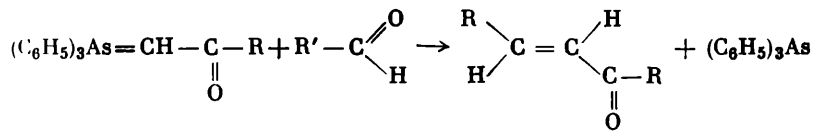
Tri-o-phenylenediarsine

Arsonium salts are reacted with bases to prepare the corresponding ylides, **arsinemethylenes**, which resemble phosphinemethylenes in many respects (Wittig reagents, see page 69); for example,



Compounds of the type given, which contain the stabilizing group

(R = alkoxyl, alkyl, or aryl) are capable of reacting with aldehydes and even with ketones with the formation of unsaturated compounds (N. A. Nesmeyanov, V. V. Pravdina):



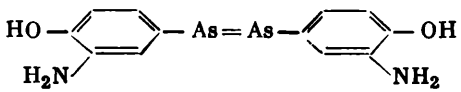
These reactions proceed hundreds of times faster than the same reactions of phosphorus ylides (which is actually the Wittig reaction) since the ylides of arsenic are considerably stronger nucleophiles. The stable arsenic ylides of the given type enter also into other reactions characteristic of the ylides of phosphorus (page 70).

Wittig prepared pentaphenylarsenic:

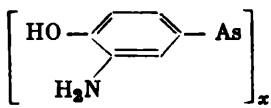
$$(C_6H_5)_4AsCl + C_6H_5Li \longrightarrow (C_6H_5)_5As + LiCl$$

This compound is thermally and chemically more stable than pentaphenylphosphorane.

3,3′-Diamino-4,4′-dihydroxyarsenobenzene played a historically important part in chemotherapy under the name of salvarsan (arsphenamine), the first effective chemotherapeutic drug against syphilis (Ehrlich). It is assigned the formula



Craft has proved that this compound is a polymer:



Organoantimony Compounds. Antimony forms the same types of compounds as arsenic.

1. Compounds of Sb(III):

$RSbH_2$, R_2SbH, R_3Sb; $RSbCl_2$, R_2SbCl;
$RSb{=}SbR$; $R_2Sb{-}SbR_2$

2. Compounds of Sb(V):

$RSbCl_4$, R_2SbCl_3, R_3SbCl_2, R_4SbCl, R_5Sb
$RSbO(OH)_2$, $R_2SbO(OH)$, R_3SbO, R_4SbOH

Antimony is linked to carbon less firmly than arsenic and even less firmly than phosphorus. This bond, however, is not destroyed by oxygen.

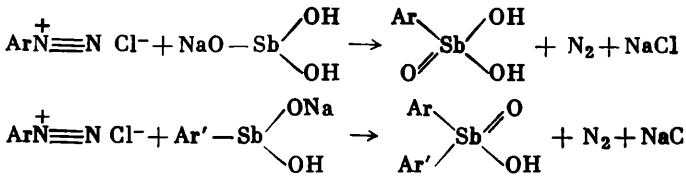
Aliphatic **stibines**, R_3Sb, are most simply prepared by the Pfeiffer method, by the action of a Grignard reagent on antimony trichloride; R_3Sb adds halogen and forms R_3SbX_2, which decomposes on pyrolysis into R_2SbX and RX. The interaction of R_2SbX with halogen leads to R_2SbX_3, the pyrolysis of which yields $RSbX_2$ and RX.

When $SbCl_5$ is added to acetylene, the compound $(ClCH{=}CH)_3SbCl_2$ is obtained in the form of a mixture of stereoisomers (*cis-* and *trans-*); their fractional distillation and reduction gives the stereoisomers $(ClCH{=}CH)_3Sb$ (A. N. Nesmeyanov, A. E. Borisov).

The aromatic compounds of antimony of the type Ar_3Sb can be produced by the Grignard reaction according to Pfeiffer or by an older method, that of Michaelis:

$$3ArCl + 6Na + SbCl_3 \longrightarrow Ar_3Sb + 6NaCl$$

As regards the compounds $ArSbCl_2$ and Ar_2SbCl, they are commonly obtained via diazo compounds by the Schmidt method (which is quite analogous to the Bart method in the arsenic series)



or by the Nesmeyanov-Kocheshkov method which has been improved by A. N. Nesmeyanov, O. A. Reutov, and O. A. Ptitsyna (depending on the reaction conditions, it is possible to obtain any of the three products as desired):

$$Ar\overset{+}{N}{\equiv}N[SbCl_4]^- + Zn \longrightarrow ArSbCl_2 \text{ (or } Ar_2SbCl, \text{ or } Ar_3Sb)$$

The reduction (more or less vigorous) of $ArSbCl_2$ gives $ArSbH_2$ or $ArSb{=}SbAr$. Like arsenobenzene, the latter is apparently a polymeric compound. By reducing Ar_2SbCl it is possible to synthesize Ar_2SbH or $Ar_2Sb{-}SbAr_2$. When $Ar'AsH_2$ is reacted with ArSbO, a mixed arsenostibino compound can be produced, whose structure is believed to be $Ar'As{=}SbAr$.

Tetraalkylstibonium salts can be synthesized by reacting trialkylstibines with alkyl iodides:

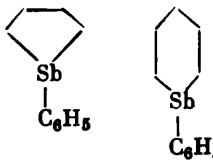
$$(CH_3)_3Sb + CH_3I \longrightarrow (CH_3)_4SbI$$

Tetraarylstibonium salts can be made, for example, by decomposing aryldiazonium borofluoride in a triarylstibine (A. N. Nes-

meyanov and L. G. Makarova):

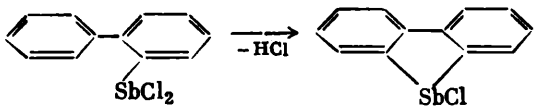
$$\overset{+}{Ar}\overset{+}{N}_2\ BF_4^- + Ar_3Sb \longrightarrow Ar_4\overset{+}{Sb}\ BF_4^- + N_2$$

A number of heterocycles with antimony as a hetero-atom have been described. For example,

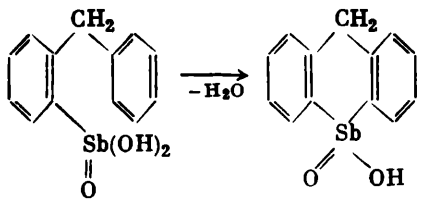


They are prepared by the action of the dimagnesium Grignard reagent $BrMg(CH_2)_nMgBr$ on phenyldichlorostibine (Grüttner and Krause).

o-Diphenylylstibine dichloride when heated loses HCl and undergoes cyclization into *o,o'*-biphenylchlorostibine (Morgan):

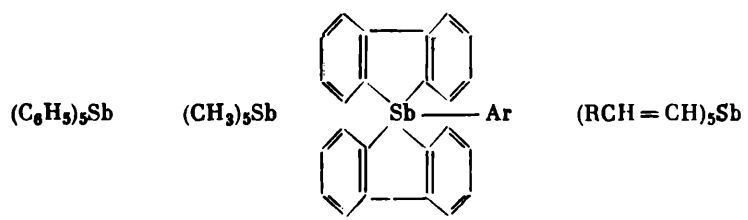


By heating *o*-benzylphenylstibinic acid with acetic anhydride and a drop of sulphuric acid Morgan obtained **stibacridinic acid**



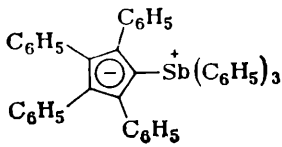
A number of organoantimony compounds have found application as chemotherapeutic drugs for the treatment of tropical diseases caused by trypanosomes and other microorganisms (sleeping sickness, leishmaniosis, kala azar, etc.). They include sodium *p*-acetylaminophenylstibnate (**stibenyl** or **stibazyl**), sodium *m*-chloro-*p*-acetylaminostibnate (**stibosan**), stibanilic acid, etc.

The following compounds of pentavalent antimony are known:



I II III IV

Compounds of the types I (prepared by Wittig) and III are also known for phosphorus and arsenic, but the antimony compounds shown are considerably more stable (thermally and chemically) than their arsenic and, the more so, phosphorus counterparts. Pentaphenylantimony when reacted with phenyllithium forms the salt $[(C_6H_5)_6Sb]^-Li^+$, in which the outer electron shell of antimony accommodates 10 electrons. In general, antimony most readily expands its outer shell during the formation of σ-bonds. The situation is different in the preparation of ylides. The increased metallic properties of the element impedes the formation of an ylide and decreases its stability. The only ylide known to exist for antimony is stabilized by the cyclopentadienyl ring and four phenyl groups:



Organobismuth Compounds. The following types of bismuth compounds are known:

$$RBiX_2, \quad R_2BiX, \quad R_3Bi, \quad R_3BiX_2, \quad R_4Bi^+ \ X^-$$

For aromatic compounds, a compound of the type Ar_5Bi has been obtained by Wittig.

Aliphatic organobismuth compounds are best prepared by the action of a Grignard reagent on bismuth trihalide (F. Hein). The trialkylbismuth obtained with excess of Grignard reagent is then subjected to the action of halogen or $BiCl_3$, the product (R_2BiCl or $RBiCl_2$) being dependent on the reagent ratio.

Aromatic compounds can be produced in the same way. With halogen it is possible to isolate R_3BiX_2, which is thermally decomposed to form R_2BiX.

Aromatic organobismuth compounds of the type Ar_3Bi can also be prepared via diazo compounds (H. Gilman; K. A. Kocheshkov, A. N. Nesmeyanov)

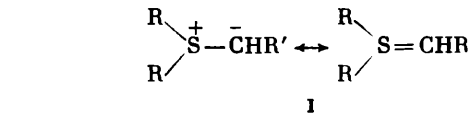
$$3(ArN_2Cl)_2 \cdot BiCl_3 + 2Bi \longrightarrow 2Ar_3Bi + 6N_2 + 3BiCl_3$$

the best results being afforded by the method developed by A. N. Nesmeyanov, T. P. Tolstaya, and L. S. Isaeva:

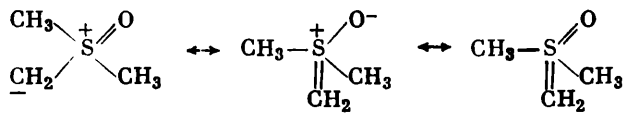
$$3ArN\equiv\overset{+}{N}\ BF_4^- + 2Bi \longrightarrow Ar_3Bi + 3N_2 + Bi(BF_4)_3$$

12.7. Group VI of the Periodic System

Sulphur Compounds. Organic compounds of sulphur have already been considered in the preceding sections. Here we shall limit our consideration to the **ylides of sulphur,** which have recently been used in the synthesis of a number of substances. Such are compounds of the types I and II:

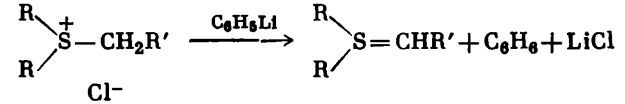


I

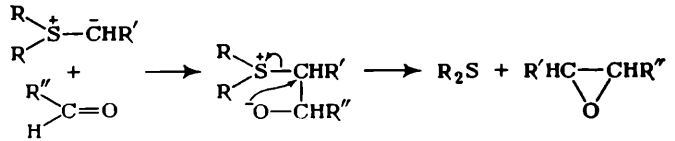


II

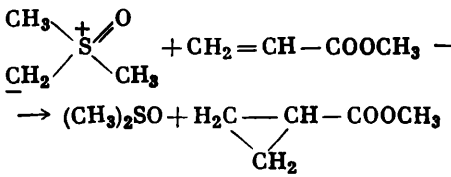
These ylides are produced in the same way as the phosphorus ylides (page 70) from the corresponding sulphonium salts by the action of strong bases. One example is:



Sulphonium ylides, in which R′ = alkyl, H, or aryl, react with aldehydes with the formation of α-oxides (epoxides):



With unsaturated compounds, especially with olefins activated by electron-attracting substituents, these ylides react with the formation of three-membered rings:



Of great importance are ylides of the type II, which are prepared simply from dimethyl sulphoxide (see Volume I, page 268).

Organoelement Compounds of Selenium and Tellurium. These compounds have found limited application and will therefore be discussed briefly.

Selenium compounds were first obtained by Wöhler. Both selenium and tellurium compounds have been largely studied by Vernon and Drew.

The most important selenium compounds are bivalent derivatives—the analogues of the corresponding sulphur compounds: RSeH, RSe—SeR, R_2Se, RSeHal.

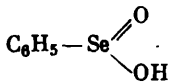
Compounds of the type RSeH are prepared, for example, by the following reaction:

$$RMgX + Se \longrightarrow RSeMgX \xrightarrow{H_2O} RSeH$$

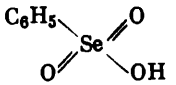
They are readily oxidized to RSe—SeR.

Dialkylselenides, R_2Se, are produced by the alkylation of Na_2Se. Compounds of the types RSeX and R_2Se add halogen, being converted into $RSeX_3$ and R_2SeX_2, respectively. The action of RI on R_2Se results in the formation of R_3SeI, trialkylselenonium iodide, a salt-like compound analogous to a sulphonium salt, in which the iodine atom can be replaced by any anion. The compound R_2Se is oxidized by $K_2Cr_2O_7$ to R_2SeO.

The aromatic organoselenium compound $C_6H_5Se—SeC_6H_5$ can be successively oxidized to **phenylseleninic** and **phenylselenonic acids**:



Phenylseleninic acid



Phenylselenonic acid

Heterocycles are known, which contain selenium as a hetero-atom, say, the analogue of thiophen, **selenophen**, which has been extensively studied by B. A. Arbuzov and Yu. K. Yuriev. In the benzene-selenophen-thiophen-furan series selenophen resembles more closely benzene in aromatic properties.

The main types of compounds for tellurium are the following: R_2Te, R_2TeX_2, $RTeX_3$ and R_3TeX.

Tellurium compounds with a valence state analogous to the valence of sulphur in sulphuric acid are hardly known.

12.8. Group VII of the Periodic System

The organoelement compounds of the halogens have been described in sufficient details in sections devoted to the halogen derivatives of the aliphatic and aromatic series. Special attention should be paid to organofluorine compounds.

Organofluorine Compounds. The chemistry of organic compounds of fluorine began to develop intensively in the forties of this century. The initial incentive was the need for materials resistant to the fluorinating action of UF_6 which was used in the separation of uranium isotopes. It turned out subsequently that organofluorine polymers, especially those completely fluorinated, are exceptionally resistant also to oxidation and various aggressive media, and some of them surpass noble metals in this respect. At present, use is made of plastics, rubbers, lubricating oils, and coatings based on organofluorine compounds and telomers. Some of the organofluorine compounds are used as refrigerants (freons) and propellants. Polyfluorinated compounds differ from ordinary organic compounds not only by the low mobility of fluorine in the organic molecule but also by the special properties of multiple bonds and functional groups in these compounds.

The nomenclature of compounds with a small number of fluorine atoms in the molecule is similar to that of other halogen derivatives. Completely fluorinated hydrocarbons are usually called **perfluoro hydrocarbons**, such as perfluoropropylene, $CF_3—CF=CF_2$, and perfluoropentane, $CF_3—(CF_2)_3—CF_3$; the names of fluorinated compounds, which have one or more hydrogen, chlorine, etc., atoms, are built in the same way as the names of perfluoro compounds in which definite fluorine atoms are replaced by hydrogen, chlorine, etc., atoms. The following two examples may be cited:

$CF_3—CF_2—CFCl—COOH$ — α-Chloroperfluorobutyric acid

$CF_3—CFH—CFH—CF_2—CF_3$ — 2,3-Dihydroperfluoropentane

Methods of Preparation. 1. *Fluorination of hydrocarbons.* The heat effect of fluorination

$$RH+F_2 \longrightarrow RF+HF \qquad \Delta H=-104 \text{ kcal}$$

considerably exceeds the heat effect of the rupture of carbon-carbon bonds. The fluorination of organic compounds with fluorine therefore leads to the degradation of an organic molecule (the end product is carbon tetrafluoride). For the fluorination reaction to be accomplished, the mixture of reacting gases is diluted with nitrogen and is passed over a copper gauze or copper turnings covered with cobalt or nickel. The copper gauze serves for removal of heat; the cobalt trifluoride formed on its surface reacts with hydrocarbons, and fluorine regenerates this higher fluoride:

$$2CoF_3+RH \longrightarrow RF+2CoF_2+HF$$
$$2CoF_2+F_2 \longrightarrow 2CoF_3$$

For a hydrogen atom to be replaced by fluorine, direct use is often made of cobalt trifluoride (NiF_3 or MnF_4 may also be employed).

2. *Electrochemical fluorination* (Simons). The method is employed, as a rule, for preparing fully fluorinated acids, amines, ethers, and certain organic compounds of sulphur. The electrolysis of a solution of an organic compound is conducted in anhydrous hydrogen fluoride (a nickel anode, voltage 5-6 V, current density ca. 0.02 A/cm^2). The fluorine formed by electrolysis displaces hydrogen atoms:

$$(CH_3CO)_2O \xrightarrow[\text{(electrolysis)}]{HF} 2CF_3COF$$

$$(CH_3)_3N \xrightarrow[\text{(electrolysis)}]{HF} (CF_3)_3N$$

The electrochemical fluorination of aliphatic hydrocarbons is hindered by their low solubility in hydrogen fluoride.

3. *Replacement of chlorine by fluorine.* The chlorine atom in organic compounds can be replaced by fluorine with the aid of SbF_3 (Swarts) and also of AgF_2 or HgF_3. The mobile halogen atoms (e.g., in α-chlorosubstituted acids or in ethylene chlorohydrin) are replaced in an exchange reaction with KF or NH_4F in polar solvents. For chlorine in alkyl chlorides to be replaced, considerably more drastic conditions are required: they must be heated with AgF_2 or HgF_3. The chlorine atom in the trichloromethyl group is replaced more easily:

$$AlkCCl_3 + SbF_3 \longrightarrow AlkCCl_2F + SbF_2Cl$$

$$ArCCl_3 + SbF_3 \longrightarrow ArCF_3 + SbCl_3$$

4. The replacement of the hydroxyl group and carbonyl carbon in alcohols, aldehydes, ketones and acids with the aid of sulphur tetrafluoride:

$$R_2C{=}O \xrightarrow{SF_4} R_2CF_2$$

$$RC(=O)OH \xrightarrow{SF_4} RCF_3$$

5. The addition of hydrogen fluoride across multiple bonds and to α-oxides (epoxides):

$$>C=C< + HF \longrightarrow >CH-CF<$$

$$H_2C-CH_2 + HF \longrightarrow HOCH_2-CH_2F$$

(O)

6. The preparation of perfluoro olefins by the dehalogenation of halopolyfluoroalkanes:

$$ClCF-CF_2 + Zn \longrightarrow ClCF{=}CF_2 + ZnCl_2$$

(Cl Cl)

This is one of the industrial methods of synthesizing trifluorochloroethylene.

7. The pyrolysis of Teflon (polytetrafluoroethylene) leads to a mixture of three main products:

$$(CF_2-CF_2)_n \xrightarrow{600-750\,^\circ C} CF_2=CF_2+CF_3-CF=CF_2+ \begin{matrix} CF_3 \\ CF_3 \end{matrix}\!\!>\!C=CF_2$$

By varying the pressure and temperature it is possible to shift the process to the side of formation of any one of these products.

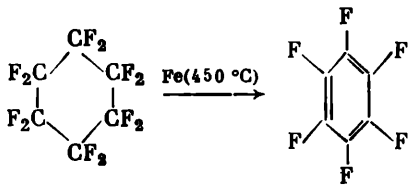
Perfluoropropylene is produced industrially by this method.

Perfluoroethylene is made by the pyrolysis of chlorodifluoromethane at 640°C:

$$2HCClF_2 \longrightarrow 2HCl+CF_2=CF_2$$

The reaction apparently proceeds via the formation of difluorocarbene.

8. The aromatic compounds of fluorine, say, fluorobenzene, are prepared by the decomposition of aryldiazonium borofluorides (Balz and Schiemann; see Volume III, page 125). Hexafluorobenzene has been obtained by the defluorination of perfluorocyclohexane on heating over powdered iron:



Properties of Fluorosubstituted Hydrocarbons. The replacement of one of the hydrogen atoms in an organic molecule by fluorine leads to a slight increase of the boiling point. On the contrary, perfluoro hydrocarbons boil below the corresponding hydrocarbons; the only exception is the first members of the homologous series. This unusual phenomenon points to the small intermolecular interactions in polyfluorinated hydrocarbons (Table 12.2). An even sharper decrease of boiling points takes place in passing from compounds with functional groups to their perfluorinated analogues. For example, acetonitrile boils at +78°C and perfluoroacetonitrile does so at —64°C.

The atomic refraction of fluorine in organic fluorine compounds is not constant and varies from 1.29 to 1.046. The small value of atomic refraction is an indication of the low polarizability of the carbon-fluorine bond. This, together with the high stability of the C—F bond (104-114 kcal/mole against 78 kcal/mole for the C—Cl bond) is responsible for the extraordinary inactivity of fluorine in its organic compounds. Particularly inert are perfluoroalkanes which

TABLE 12.2 **Boiling Points of Fluorinated Hydrocarbons**
(for comparison, the boiling points of hydrocarbons are given in parenthesis)

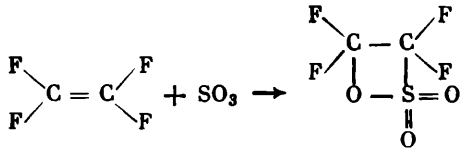
Formula	b.p., °C	Formula	b.p., °C
I. Saturated			
CF_4	−128 (−161.5)	n-C_6F_{14}	58 (68.7)
C_2F_6	−79 (−88.6)	n-C_7F_{16}	82 (98.4)
n-C_3F_8	−39 (−42.1)	n-C_8F_{18}	—
n-C_4F_{10}	+1 (−0.5)	n-C_9F_{20}	125 (150.8)
n-C_5F_{12}	+30 (+36.1)	n-$C_{10}F_{22}$	238-240 (286.8)
II. Unsaturated			
$CF_2=CF_2$	−76	$CF_3-CF=CF_2$	−29
$CH_2=CF_2$	−82	$CF_3-CH=CH_2$	−28.3
$CH_2=CHF$	−72	$CF_3-CH=CHF$	−16
$CHF=CF_2$	−51	$CF_3-CF_2-CF=CF_2$	+1
$CF_2=CFCl$	−26.8	$CF_3-CF=CF-CF_3$	0
$CFCl=CFCl$	−22	$(CF_3)_2C=CF_2$	+7
$CF_2=CFBr$	+2	$CF_3-(CF_2)_2-CF=CF_2$	+30

do not enter into substitution reactions at all. The other halogen atoms in perfluorinated compounds (but not in polyfluorohalogenobenzenes) are also inert, but to a lesser extent. For example, compounds of the type CF_3-CF_2I give organomagnesium compounds, CF_3-CF_2-MgI (recall that compounds such as CCl_3Br or CH_2Cl-CH_2Br are not capable of forming organomagnesium compounds; for example, from CH_2Cl-CH_2Br there is obtained ethylene instead).

Fluorine-containing olefins are able to add strong electrophiles, but the rate of such addition is lower than in the case of ordinary olefins, and falls rapidly as the number of fluorine atoms at a double bond or next to it increases. The fluorine at a double bond orients the addition of hydrogen halide in the same manner as does the chlorine atom (and for the same reasons):

$$CH_2=CF_2+HF \longrightarrow CH_3-CF_3$$

Sulphuric anhydride adds on to perfluoroolefins with the formation of β-sultones (the analogues of β-lactones):



In anhydrous hydrofluoric acid, nitric acid dissociates with the formation of the nitronium cation. Under these conditions there takes place a conjugate addition of the nitronium ion and the fluoride ion at the double bond:

$$HF + 2HNO_3 \rightarrow H_3O^+ + F^- + NO_2^+ + NO_3^-$$

$$CF_2=CF_2 + NO_2^+ + F^- \rightarrow CF_3-CF_2NO_2$$

The reactions particularly characteristic of perfluoroolefins are reactions of nucleophilic addition, say, of alcohols and amines, with the formation of ethers and amines:

$$CF_2=CF_2 + HOR \rightarrow CHF_2-CF_2OR \rightarrow CF_2=CF-OR + HF$$

$$CF_2=CF_2 + R_2NH \rightarrow CHF_2-CF_2-NR_2$$

These reactions unusual for olefins occur as a result of the extreme impoverishment of the double bond in electrons because of the presence of fluorine atoms. Naturally, in the following series the tendency to undergo nucleophilic additions increases and that to add electrophilic reagents decreases:

$$CF_2=CF-OR \quad CH_2=CF_2 \quad CF_2=CF_2 \quad CF_3-CF=CF_2 \quad (CF_3)_2C=CF_2$$

It has been found that hydrogen fluoride (and also nitrosyl fluoride) add on to the first members of this series by an electrophilic mechanism and to the last members by a nucleophilic mechanism (I. L. Knunyants, B. L. Dyatkin). The rate of addition of hydrogen fluoride falls in this series and increases again for perfluoroisobutylene.

1. Electrophilic addition:

$$H^+CF_2=CF-\ddot{O}R \underset{}{\overset{\text{slow}}{\rightleftharpoons}} HCF_2-\overset{+}{C}F-\ddot{O}R \xrightarrow[\text{fast}]{F^-} HCF_2-CF_2OR$$

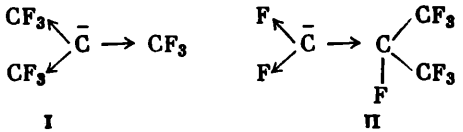
2. Nucleophilic addition:

$$\begin{matrix} CF_3 \\ CF_3 \end{matrix}\!\!>\!C=CF_2 + F^- \underset{}{\overset{\text{slow}}{\rightleftharpoons}} \begin{matrix} CF_3 \\ CF_3 \end{matrix}\!\!>\!\overset{-}{C} \rightarrow CF_3 \xrightarrow[\text{fast}]{H^+} \begin{matrix} CF_3 \\ CF_3 \end{matrix}\!\!>\!CH-CF_3$$

This reaction is catalysed by fluorides; it means that the overall rate of the reaction is determined by the addition of the fluoride ion to the double bond. The situation is the same with addition of nitrosyl fluoride, $\overset{\delta-}{F}-\overset{\delta+}{NO}$: in the presence of potassium fluoride it adds more rapidly to perfluoropropylene and perfluoroisobutylene.

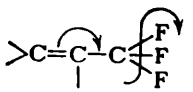
The orientation in nucleophilic addition to perfluoroolefins is accounted for as follows. The trifluoromethyl groups are stronger electron-acceptors than the fluorine atom, and therefore the negative

charge in the anion I is delocalized more strongly than in the anion II.



I II

Thus, at the first stage of addition of nitrosyl fluoride or hydrogen fluoride, perfluoroisobutylene forms the more energetically favourable anion II (to which there is further added the corresponding cation). According to Knunyants, this is accounted for by the conjugation of the σ-bonds of fluorine atoms in trifluoromethyl groups with π-bonds or with a negative charge (an electron pair):



Perfluoroolefins are capable of free-radical additions. Thus, they add chlorine or bromine only by a free-radical mechanism upon illumination. Nitrogen dioxide adds in the same way:

$$CF_2=CF_2-2\cdot NO_2 \xrightarrow{h\nu} O_2N-CF_2-CF_2-ONO+O_2N-CF_2-CF_2-NO_2$$

The free-radical character is also displayed by the polymerization or copolymerization of perfluoroolefins:

$$nCF_2=CF_2 \longrightarrow \cdots-(-CF_2-CF_2-)_n-\cdots$$

Unlike perfluoroisobutylene, perfluoropropylene is capable of copolymerization with ordinary olefins.

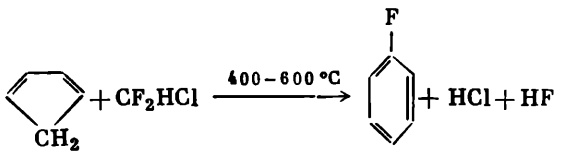
The most important among polymers is **polytetrafluoroethylene** (Teflon or Fluon), a thermoplastic with a softening point of about 425°C. It is absolutely inert to acids, alkalis, and oxidizing agents (with the exception of fluorine). Teflon is used for the production of chemically resistant vessels, machine parts, and for application of corrosion-resistant coatings to metallic surfaces. Teflon has a very low friction coefficient and is employed for the manufacture of friction surfaces (of pistons, etc.). Another starting material used for the production of plastics is **trifluorochloroethylene** which is synthesized according to the following scheme:

$$CCl_3-CCl_3 \xrightarrow{SbF_3} CClF_2-CFCl_2 \xrightarrow{Zn} CF_2=CFCl$$

Trifluorochloroethylene oligomers are employed as chemically stable lubricating oils. Chemically stable fluorinated rubbers are manufactured by the copolymerization of perfluoropropylene with difluoroethylene and other fluorinated olefins.

The chemistry of fluoroaromatic compounds began to develop intensively somewhat later than the chemistry of organic fluorine compounds of the aliphatic series. The fluorine derivatives of the aromatic series are less important industrially than those of the aliphatic series.

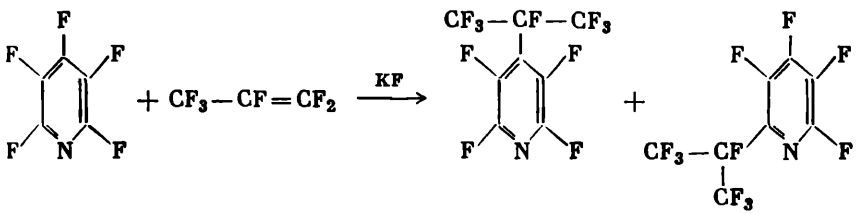
Fluorobenzene is used for the synthesis of certain drugs. One of the most interesting methods of preparation of this compound is by heating a mixture of cyclopentadiene with substances which form difluorocarbene (O. M. Nefedov):



2,4-Dinitrofluorobenzene in which the fluorine atom is very readily replaced by a nucleophilic mechanism is used as the reagent for dinitrophenylation, for example, in the investigation of proteins. Some aromatic fluorine derivatives have been proposed as starting materials for the synthesis of dyes.

Hexafluorobenzene can be used as a solvent for scintillators, as a working medium or a heat-transfer agent in power plants, and also as an inhalation anesthetic.

A specific "nucleophilic version" of the Friedel-Crafts reaction is the method of alkylation of perfluoroaromatic compounds by fluoroolefins in the presence of potassium fluoride as a catalyst:



The first act of the reaction is the nucleophilic attack of the perfluoroolefin by the fluoride ion. The perfluoroalkyl anion formed displaces, by a nucleophilic mechanism, one of the fluorine atoms in the aromatic ring. This reaction is, so to say, the converse of the Friedel-Crafts reaction between aromatic compounds and olefins in the presence of Lewis acids. In the classical Friedel-Crafts reaction, the role of a catalyst boils down to inducing a positive charge on the attacking particle; the hydrogen is replaced, being removed as a proton. In the reaction given above, which was discovered by Chambers, the attacking particle is an anion, and the fluorine atom being replaced is removed as an anion.

In contrast to perchlorovinyl groups, perfluorovinyl groups exchange fluorine for an organic radical under the action of lithium aryls (K. A. Kocheshkov, T. V. Talalaeva):

$$ArCF=CF_2+LiC_6H_4Li\text{-}p \longrightarrow ArCF=CF-C_6H_4-CF=CFAr\text{-}p$$

Fluorine-Containing Compounds with Functional Groups. Fluorinated compounds containing functional groups are prepared either by electrochemical fluorination (page 92), by replacement of chlorine atoms by fluorine, or from perfluoroolefins. The oxidation of perfluoroolefins may yield acids or ketones:

$$CF_3-CF_2-CF=CF_2 \xrightarrow{KMnO_4(H_2O)} CF_3-CF_2-COOH$$

$$\begin{matrix}CF_3\\CF_3\end{matrix}\!\!>\!C=CF_2 \xrightarrow{KMnO_4} \begin{matrix}CF_3\\CF_3\end{matrix}\!\!>\!C=O$$

The latter method is the most convenient for the preparation of perfluoroketones.

When perfluoroolefins are oxidized in alkaline medium, α-oxides can be obtained:

$$CF_3-CF-CF_2$$
$$\quad\quad\diagdown\ \diagup$$
$$\quad\quad\ O$$

Nitroso and nitro compounds can be produced by the conjugate addition of the corresponding groups to double bonds, as has been pointed out above. When alcohols and amines are added to perfluoroolefins, fluorinated ethers and amines are produced.

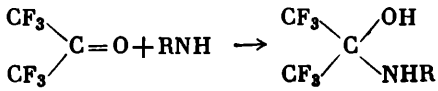
The properties of fluorinated acids, ketones, alcohols, amines, etc., are closely associated with the electron-attracting effect of fluorine atoms and are therefore sharply pronounced in the case of perfluoro derivatives, whose properties will be discussed here. The negative inductive effect of fluorine has a bearing primarily on the acidity and basicity of functional groups. Thus, perfluorotriethylamine is not a base, and fluorinated alcohols are weak acids. Below are given the values of pK_a in aqueous solution (I. L. Knunyants, B. L. Dyatkin, N. P. Gambaryan, E. M. Rokhlin):

CF_3CH_2OH . . . 12.8 $(CF_3)_2CHOH$ . . . 9.3 $(CF_3)_3COH$ . . . 5.4

The properties of perfluoroketones have also been studied by Knunyants and his co-workers. These compounds have an exceedingly reactive carbonyl group. Thus, they are capable of adding water or alcohols, forming very stable hydrates or semi-acetals:

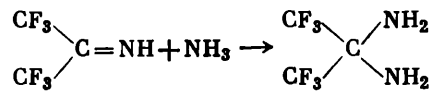
$$\begin{matrix}CF_3\\CF_3\end{matrix}\!\!>\!C\!<\!\begin{matrix}OH\\OH\end{matrix} \qquad \begin{matrix}CF_3\\CF_3\end{matrix}\!\!>\!C\!<\!\begin{matrix}OH\\OR\end{matrix}$$

Such adducts do not lose water or alcohol even when heated in vacuum. Hydrates of the perfluoroacetone hydrate type are weak acids (comparable in strength to acetic acid). Perfluoroketones give stable adducts with ammonia and amines:



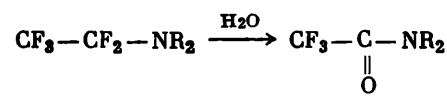
which are distilled even without dehydration.

The imine of hexafluoroacetone adds ammonia, forming a geminal diamine, a rare combination of atoms in organic chemistry:



As can be seen, molecules containing, at the same carbon atom, a hydroxyl and an amino group, two amino groups, two hydroxyl groups, a hydroxyl and fluorine are common in the organic chemistry of perfluorinated compounds. The stability of such geminal compounds is attributed to the difficulty of detachment of the anion (—OR, —OH, —NH_2) from the positively charged carbon atom.

As has already been pointed out, when alcohols and amines are added to perfluoroolefins, ethers and amines are obtained. In these compounds, the geminal fluorine α-atoms are rather mobile and can be hydrolysed to form derivatives of fluorocarboxylic acids:



Fluorine-containing carboxylic acids show high dissociation constants:

	$K_a \times 10^{-5}$ (at 20°C)
CH_3COOH	1.8
FCH_2COOH	220
$F_2CHCOOH$	57,000
CF_3COOH	59,000
$CF_3(CF_2)_2COOH$	68,000

Trifluorocarboxylic acid is comparable to strong mineral acids in regard to dissociation constants. This acid and its anhydride are used for protection of amino and hydroxy groups by acylation since trifluoroacetyl protection is easily destroyed by hydrolysis. The mixed anhydrides of trifluoroacetic acid and other organic acids are good acylating agents, in which case it is exactly the acyls of

ordinary organic acids that take the place of hydrogen in compounds being acylated. Trifluoroacetic acid is sometimes used as a polar protic solvent.

12.9. Organometallic Compounds of Transition Metals

Transition metals with empty *d*-electron levels do not form stable alkyl and aryl derivatives (with the exception of platinum). In this respect, the metals of the 2nd subgroup of Group I—copper, silver, gold—occupy a special position. They complete the long periods, their *d*-levels are filled, but the *d*-electrons are still capable of participating in chemical transformations. The organometallic compounds formed by these metals are related to compounds of transition elements. Copper and silver are able to form extremely unstable aliphatic derivatives RCu and RAg, which are prepared by the action of a Grignard reagent on CuI and AgCl on strong cooling but are decomposed even at relatively low temperatures. More stable are the following compounds obtained in this way: phenylsilver, C_6H_5Ag, which however decomposes already at —18°C, and phenylcopper, C_6H_5Cu, which decomposes at +80°C. Even more stable are the organometallic compounds of trivalent gold, of which the following types are known (Pope and Gibson): $[RAuCl_2]_2$ and $[R_2AuCl]_2$. The first compound can be synthesized not only by the Grignard reaction but also by direct **auriation** in the aromatic series—by the action of $AuCl_3$ on aromatic compounds (**Kharasch**):

$$AuCl_3 + C_6H_6 \longrightarrow C_6H_5AuCl_2 + HCl$$

A number of organogold compounds of the aliphatic, aromatic and heterocyclic series are known. These compounds are stable not only to water but also to acids and air. Organometallic derivatives of univalent gold have also been produced, but invariably with the second ligand being linked by a coordinate bond:

$$CH_3Au \cdot P(C_2H_5)_3 \text{ (m.p. 62°C)};$$
$$C_6H_5Au \cdot P(C_6H_5)_3 \text{ (dec. p. 152°C), etc.}$$

With olefins, univalent gold forms π-complexes, $AuCl \cdot C_nH_{2n}$, which are obtained by the action of an olefin (in excess) on $HAuCl_4$ in aqueous solution. In this reaction, Au(III) is reduced to Au(I) and a π-complex separates out as a precipitate. Only compounds with cycloalkenes have been described (Hüttel, 1965).

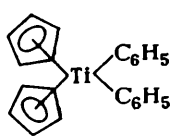
As noted above, transition metals (with the exception of platinum and, to a certain extent, titanium) do not form stable alkyl and even aryl compounds unless their empty *d*-electron levels are filled in

this or that way. In this case, alkyl or aryl compounds are obtained, but they are still relatively slightly stable.

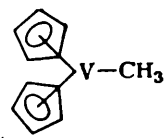
As a typical example, we shall cite compounds of chromium. The halides of trivalent chromium do not give aliphatic organometallic compounds, for example, when allowed to react with a Grignard reagent obtained from alkyl halides or a benzyl halide. But the action of benzyl chloride on an aqueous solution of divalent chromium hydrate leads to the formation of an unusual hydrate of an organometallic cation, benzylchromium, which owes its existence to the filling of the *d*-levels of chromium due to the complexed water molecules:

$$C_6H_5CH_2Cl + 2Cr(OH_2)_6Cl_2 \longrightarrow [C_6H_5CH_2Cr(OH_2)_5]Cl_2 + Cr(OH_2)_6Cl_3 + H_2O$$

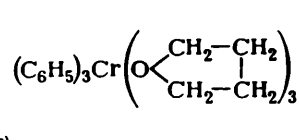
Further examples of stabilization of the alkyl derivatives of transition metals due to the filling of their *d*-levels through complex-formation are as follows (for more detail, see page 129):



(decomposes slowly at 20 °C and rapidly at 100 °C)

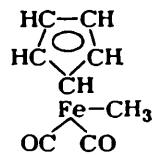


(decomposes at 80-100 °C)

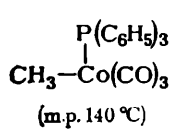


$CH_3Mn(CO)_5$

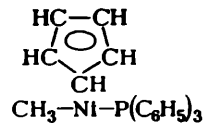
(m.p. 95 °C)



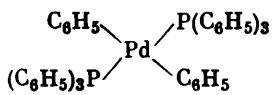
(decomposes at 78-82 °C)



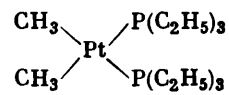
(m.p. 140 °C)



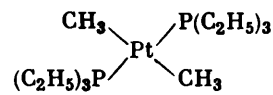
(m.p. 115-118 °C)



(m.p. 99-100 °C)



cis-Isomer (m.p. 81-82 °C)



trans-Isomer (m.p. 76-79 °C)

(divalent Pd and Pt, square coordination)

As regards the organometallic compounds of transition metals with alkyls or aryls without ligands occupying the *d*-levels of the metal, as far back as 1907 Pope and Peachey obtained $(CH_3)_3PtI$ by the action of methylmagnesium iodide on platinum chloride, and Gilman isolated CH_3PtI_3, $(CH_3)_2PtI_2$, and $(CH_3)_4Pt$. These compounds are all rather stable. Tetramethylplatinum is a colourless, benzene-soluble substance.

After several decades of unsuccessful attempts there followed the unexpected synthesis of CH_3TiCl_3 and $C_2H_5TiCl_3$ effected by the

action of the corresponding aluminium alkyls on $TiCl_4$. The reaction is conducted at —80°C, but even at room temperature these compounds are stable for some time; $(CH_3)_2TiCl_2$ is less stable, and $(CH_3)_4Ti$ is stable only at a temperature below —78°C. All these compounds have been obtained in the form of violet crystals, which is apparently due to the presence of an impurity of trivalent titanium. Dimethyl- and diphenylmanganese have also been described; they have been prepared at a low temperature.

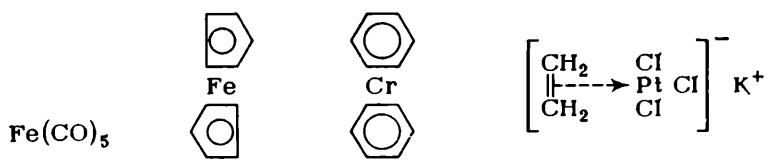
$$2RLi + MnI_2 \longrightarrow R_2Mn + 2LiI$$

The unstable compound CH_3MnI has been produced in an analogous way.

Diphenylmanganese, like all aromatic compounds, is more stable than its aliphatic analogue. Dimethylmanganese is an explosive powder which does not dissolve at all and is spontaneously flammable in air.

The self-decomposition of other alkyl and aryl compounds of transition metals in reactive solutions of their salts and a Grignard reagent has already been described (see page 33, Kharasch experiments).

Whereas alkyl and aryl compounds constitute the only type of true organometallic compounds for non-transition metals, i.e., compounds with a metal-carbon bond, the situation is quite different with transition metals. The principal types of organometallic compounds of transition metals are the following: (a) metal carbonyls, say, iron pentacarbonyl; (b) cyclopentadienyl sandwich derivatives—**metallocenes** (e.g., dicyclopentadienyliron or ferrocene, page 129, and the π-cyclopentadienyl derivatives of other metals given on the same page); (c) **metalloarenes**, i.e., complexes of a transition metal with aromatic molecules, say, dibenzenechromium (see page 125); (d) olefinic (dienic, etc.) π-complexes, an example of which is the long-known **Zeise's salt** (page 117):



Iron pentacarbonyl Dicyclopentadienyliron Dibenzenechromium Zeise's salt

There are also mixed compounds consisting of all these types: **arenecarbonyls, metallocenecarbonyls, arenemetallocenes**, etc. We shall briefly discuss the organometallic compounds of transition metals in the order indicated, the discussion being preceded by certain considerations.

Even from the formulas of metal carbonyls $Fe(CO)_5$, $Co_2(CO)_8$, $Ni(CO)_4$, $Cr(CO)_6$, and arenes (see dibenzenechromium) it is clearly seen that the old well-established valence concepts are inapplicable to these compounds. This is the same problem that faces the inorganic chemist in studying the complex compounds of transition metals and which already at the beginning of this century led to the necessity of introducing the concept of the coordination number.

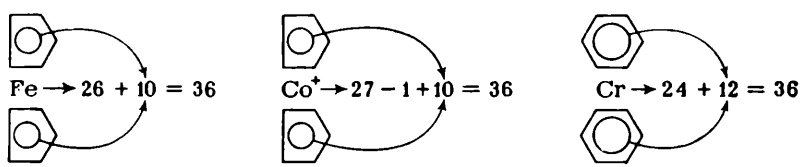
Though, in principle, each individual compound is a special case, certain empirical qualitative regularities can however be traced, which are not obeyed quite strictly but which enable one to orient in the field of these compounds without special calculations.

1. The effective atomic number rule (Sidgwick). The ligands CO, C_5H_5, C_6H_6, olefins, etc., add on to a transition metal, filling its electron shell to attain the nearest rare gas structure. Each molecule of CO or an olefin (and also amines, phosphines, esters of phosphorous acid, etc.) supplies two electrons to the metal, each cyclopentadienyl, five, and each benzene ring, six. Below is given, for some metal carbonyls, the number of electrons per metal atom (the sum of its own electrons and those supplied by the ligand):

$V_2(CO)_{12}$	$Cr(CO)_6$	$Mn_2(CO)_{10}$
$23+12=35$	$24+12=36$	$25+10=35$
$Fe(CO)_5$	$Co_2(CO)_8$	$Ni(CO)_4$
$26+10=36$	$27+8=35$	$28+8=36$

As seen from the calculation, the effective atomic number in carbonyls (i.e., the number of electrons in the outer shell of the metal) is actually equal to the atomic number of the nearest inert gas—crypton (36). For metals with an odd atomic number (V, Mn, Co) the sum of electrons per metal atom is only 35, and the effective atomic number equal to the atomic number of crypton is obtained by doubling the molecule and by sharing a pair of electrons by metal atoms. This can also be achieved by capturing one electron from the atom of an alkali metal or a hydrogen atom in compounds of the type $H_2Fe(CO)_4$ or $NaMn(CO)_5$.

The same calculation is valid for the most stable sandwich compounds—ferrocene, cobalticenium ion, dibenzenechromium:

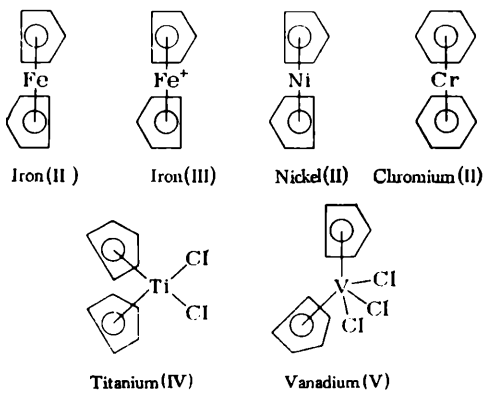


The effective atomic number rule, however, determines only the most stable systems. There are a great number of substances, whose

number of electrons is greater and, particularly often, less than the number of electrons in the nearest inert gas. Such are, for example, the cation corresponding to ferrocene—the ferricenium ion with 35 electrons, and neutral cobaltocene with 37 electrons.

In compounds, such as carbonyls and dibenzenechromium, which consist of a metal atom and molecules capable of independent existence (CO and C_6H_6 in our examples), the metal is formally considered to be zero-valent. The conditionality of this definition is obvious. According to Sidgwick, valency may be defined as the number of electrons donated by an atom to its partner (complete donation or equal sharing of electrons). If it is assumed that in the compounds under consideration the ligand alone supplies electrons and the metal retains its own electrons, then the null valency of the metal is consistent with Sidgwick's definition. In fact, however, the electrons of the metal, particularly the electrons of the *d*-levels, do participate in bond formation (**back-donation**—the reverse transfer of electrons from the metal)*.

2. In sandwich cenes (and arenes), the ordinary formal valency of the metal seems to be retained, despite the delocalization, if only it is assumed that one unit of valency is utilized for addition of a ring to the metal, as is clear from the following comparisons:

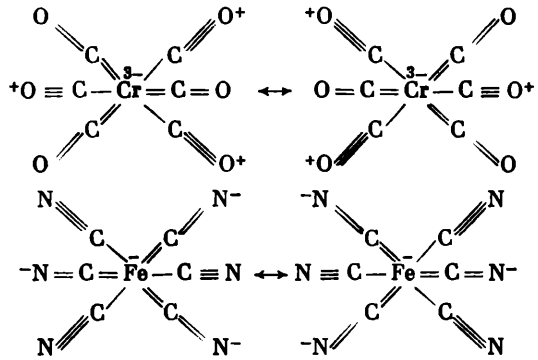


As we have already seen in the case of organoboron and organoaluminium compounds and also of all the above types of organometallic compounds of transition metals, the use of the language of the valence bond method for describing their electronic structure presents great difficulties. Even a purely qualitative description usually requires the consideration of a large number of resonance structures. Thus, Pauling examines 560 resonance structures grouped into 11 classes

* This type of bonding is also sometimes called ***metal-to-ligand π-bonding*** or *back bonding.— Tr.*

for the ferrocene molecule, only the covalent structures being included; he introduced simplifying assumptions on the contributions of the structures.

In the valence bond method, use is made of the hybridization of the orbitals of a metal, as has already been described (see Volume I, page 318) for carbon in its various valence states: sp^3, sp^2, sp. In the case of transition metals, apart from the s- and p-orbitals, the d-orbitals also undergo hybridization. For example, the most ordinary octahedral type of complex has d^2sp^3-hybridized orbitals of the metal, which are directed along the axes of the octahedron; the square type of complex (e.g., many compounds of nickel, palladium and divalent platinum, say, Zeise's salt, $[C_2H_4PtCl_3]^-K^+$) is regarded as having dsp^2-hybridized orbitals of the metal; tetrahedral complexes, such as nickel carbonyl, have sp^3-hybridized metal orbitals. A hybridization of the dsp^3 type forms the basis of trigonal-bipyramidal complexes of the type $Fe(CO)_5$. Thus, the number of hybridization-equilibrated orbitals of the metal contained in the compound is equal to its coordination number. However, a number of arguments, especially the low probability of a high negative charge on the metal in carbonyls or in the anion $Fe(CN)^{4-}$ upon assumption of a single bond between the metal and each of the CO groups or four CN groups, and data on the decreased M—C distance and increased C—O distance lead us to assume a certain degree of double-bond character of the linkage between the metal and the carbon atom of CO and CN groups as a result of the donation of electrons by the metal. In virtue of this, for a number of complexes, use has to be made of the concept of resonance with participation of structures containing double M=C bonds. For instance, the following structures are given for chromium hexacarbonyl and ferricyanide ion:



Much more fruitful here is the molecular orbital method (see Volume I, page 307). From the standpoint of the molecular-orbital treatment of the electronic structure of the organometallic compounds of transition metals under discussion, the bonds between the ligands

and the metal are formed by a common system of electrons, the distribution of which over the molecular orbitals and the corresponding orbital-energy levels is determined by the condition of a minimum of total energy of this system of electrons. Thus, organometallic compounds of this type contain delocalized bonds between the metal and the ligands.

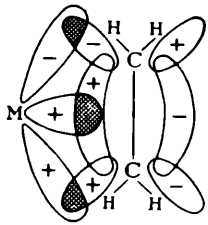


Fig. 12.9.
The formation of an octahedral complex.

Let us consider the molecular-orbital approach to the description of the electronic structure of the most frequently encountered octahedral (Fig. 12.9) complexes of transition metals. Let these be the

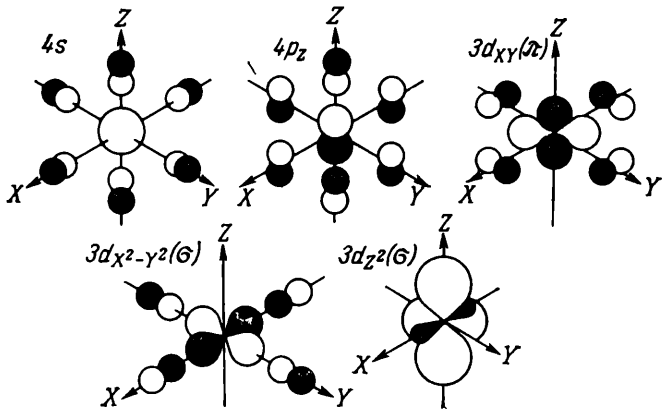


Fig. 12.10.
The atomic orbitals of transition metals, which take part in the formation of molecular orbitals of octahedral complexes. The filled circles are regions of negative values of the orbital wave functions.

metals Cr, Mn, Fe, Co with their $3d$, $4s$, and $4p$ atomic orbitals, which are to be united into molecular orbitals with electron pairs being transferred to the metal of the ligands. These may be the unshared electron pairs of oxygen, sulphur, nitrogen, phosphorus, carbon monoxide, etc., or the π-pairs of olefins, aromatic rings, etc. Figu-

re 12.10 shows the atomic orbitals of transition metals, which are utilized for the formation of an octahedral complex, and the approaching electron orbitals of the ligands, which participate in the building of molecular orbitals. Only the $3dz^2$ orbital is shown without the orbitals of the ligand approaching it.

The different types of overlap of the orbitals of the metal and ligand and the different character of the symmetry of the total molecular orbital are responsible for the so-called σ-, or π-, or δ-character. The wave function of the σ-orbital does not change sign upon 180° rotation about the symmetry axis. The wave function of the π-orbital changes its sign on such rotation. The wave function of the δ-orbital changes its sign twice upon 180° rotation.

For organometallic complexes it is essential that the metal not only accepts the electrons of the ligand on the molecular orbitals of the complex, the formation of which involves *d*-orbitals, but also donates its *d*-electrons to the new molecular orbitals of the ligand. These orbitals are formed by the overlap of the non-bonding orbitals of the ligand and the *d*-orbitals of the metal, as shown, for example, in Fig. 12.9 for a complex formed by a metal and an olefin. This ability to accept electrons from a metal (back-donation) is exhibited by such ligands as olefins, arenes, phosphines, carbon monoxide, but not by ammonia or water molecules, which accounts for the high stability of carbonyl, phosphine and other complexes with back-donation of electrons.

Figure 12.10 shows the 4*s*-, *p*-, and *d*-orbitals of the atoms (*s*-orbitals are known to have a spherical shape with the coordinate origin at the centre). The only representative shown for three *p*-orbitals is the p_z-orbital; the p_x- and p_y-orbitals, which are also sphere-shaped, are formed from the p_z-orbital by 90° rotation in the space around the *X* and *Y* axes. In just the same manner, of the three d_{xy}, d_{xz}, and d_{yz} orbitals only the d_{xy} orbital, which forms a molecular orbital of the π-character, is shown. The remaining orbitals (d_{xz} and d_{yz}) are also formed from it by spatial rotation around 90°. The two remaining *d*-orbitals, namely $d_{x^2-y^2}$ and d_{z^2}, are given at the bottom of the figure. Addition of the atomic orbital (i.e., the ψ-function) of the metal and the orbital of the ligand gives a **bonding molecular orbital.** Subtraction of the atomic orbital of the metal from the orbital of the ligand yields an **antibonding molecular orbital** which is filled by electrons in the excited state of the molecule.

Molecular orbitals of the σ-type, as designated in Fig. 12.10 and seen from the mode of overlap (cylindrical symmetry), are built up of the following orbitals: $d_{x^2-y^2}$, d_{z^2}, *s*, p_x, p_y and p_z.

Note that in the valence bond method this group of orbitals is regarded as hybridized (d^2sp^3-hybridization) into six equivalent orbitals oriented along the axes of the octahedron, each including a pair of bonding electrons.

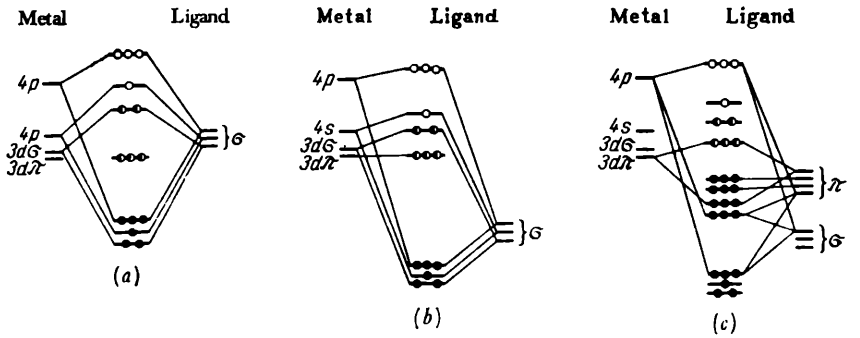


Fig. 12.11.
Energy-level diagrams for transition-metal complexes of the MX_6 type:
a—non-polar bonds; b—polar bonds; c—the π-bond is included. The filled circles represent orbitals that are occupied by electron pairs; the unfilled circles are antibonding vacant orbitals; the half-filled circles are orbitals that may be filled by an electron pair or an electron or remain vacant, depending on the metal and the ionic state.

Bonds of the π-type may be formed by *p*- as well as d_{xy}-, d_{xz}-, and d_{yz}-atomic orbitals of the metal. The correlation diagrams given illustrate what has been said above for the absence of π-bonds as well as for their presence. In Fig. 12.11, which refers to the complex compounds of the type MX_6, the thick horizontal lines designate the energy levels of the corresponding molecular orbital (in the middle of the figure), the energy levels of the orbitals of the metal and the ligand being arranged on the left and right sides, respectively. The filled circles in the middle part of the figures are the invariably filled molecular orbitals formed by combination of the corresponding atomic orbital of the metal and the orbital of the ligand. The half-filled circles represent the orbitals which may and may not be filled by electrons. Here belong *d*-electrons which are so characteristic of transition metals with their variable valency and which are responsible for their characteristic magnetic and spectral properties.

Figure 12.11*a* differs from Fig. 12.11*b* by a presentation of the non-polar bonds formed by the increasing positive charge on the metal atom. As examples may be cited the various octahedral inorganic complexes of transition metals. The participation of the π-orbitals of the ligand is often manifested in inorganic complexes, especially in organometallic compounds of transition metals. This particularly important case is shown in a general form in Fig. 12.11*c*.

A. Metal Carbonyls

There are metal carbonyls of the following types: carbonyls containing no bridge carbon-monoxide groups between the metals; carbonyls invariably containing two or more metal atoms linked

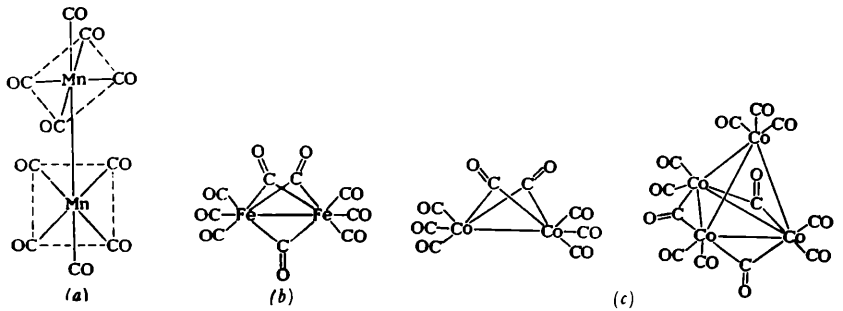


Fig. 12.12.

The structure of metal carbonyls:

a—manganese carbonyl; *b*—iron carbonyl; *c*—cobalt carbonyl (octacarbonyl and dodecacarbonyl).

by $\diagdown$C=O$\diagup$ bridges, each of which donates one bonding electron to each of the metal atoms bound; carbonyls in which three metal atoms are united by one molecule of carbon monoxide. Besides, in many such polynuclear carbonyls, just as in the simplest dimeric carbonyls, such as $[Mn(CO)_5]_2$ and $[Co(CO)_4]_2$, dimerization is effected owing to the direct bonding between the metal atoms.

The composition and physical properties of a number of carbonyls are given in Table 12.3.

The structure of carbonyls is established by X-ray structure analysis. Moreover, an indication of the presence of bridging carbon-monoxide groups is afforded by infrared spectroscopy (bridging groups have a frequency lower than 1900 cm^{-1}, and the frequency of carbon monoxide linked to one metal atom is about 2000 cm^{-1}). The absence of unpaired electrons is deduced from the absence of a magnetic moment; the direct metal-metal linkage is deduced from the value of the M—M distance measured by X-ray or electron diffraction methods. Examples illustrating the structure of carbonyls are given in Fig. 12.12.

Nickel and iron carbonyls are most readily prepared by the direct action of carbon monoxide on the metal (the reaction is more rapid if the metal is finely divided and a high pressure is used). Thus, in 1890 Mond discovered nickel carbonyl (tetracarbonylnickel), a volatile compound which readily decomposes with the formation of the pure metal and is unfortunately very toxic. The discovery of nickel carbonyl led to its extensive use in metallurgy. **Iron pentacarbonyl** is also used for the production of the purest iron. Carbonyls of other metals are not, however, produced so simply. In most of the cases, salts of a metal have to be reacted with carbon monoxide under pressure at the moment of their reduction, usually in a non-aqueous me-

TABLE 12.3.

	V	VI	VII
4	$V(CO)_6$ blue, sublimes at 45-60°C (10 mm Hg) $\underline{V_2(CO)_{12}}$ orange	$Cr(CO)_6$ colourless, solid, distils with steam	$\underline{[Mn(CO)_5]_2}$ goldish, m.p. 154-155°C (sublimes)
5		$Mo(CO)_6$ colourless, sublimes, distils with steam	
6		$W(CO)_6$ colourless, sublimes, distils with steam	$\underline{[Re(CO)_5]_2}$ colourless, m. p. 177°C (sublimes)

Note: Carbonyls with a metal-metal bond are underlined by a single line; a double

dium. Job and Cassal were the first to obtain, in this way, the **hexacarbonyls of chromium, molybdenum,** and **tungsten,** using a Grignard reagent. A. N. Nesmeyanov, K. A. Kocheshkov, and K. N. Anisimov successfully used zinc dust instead of the Grignard reagent. **Manganese carbonyl** discovered by Brimm is best prepared by using sodium benzophenone ketyl, $(C_6H_5)_2CONa$, as a reducing agent (Closson).

Polynuclear carbonyls with carbon-monoxide bridges are produced from simple carbonyls as the result of loss of CO, usually by the action of light:

$$2Fe(CO)_5 \xrightarrow{h\nu} Fe_2(CO)_9 + CO$$

or on heating

$$6Fe_2(CO)_9 \xrightarrow{95°C} 2Fe_3(CO)_{12} + 6Fe(CO)_5$$

Fundamental studies in the field of metal carbonyls are due to W. Hieber and his school (E. O. Fischer and others).

Metal Carbonyls

VIII	
$Fe(CO)_5$ yellow-brown, m. p. −20°C, b. p. +103°C	$Ni(CO)_4$ colourless, m. p. −25°C, b. p. +43°C
$\underline{\underline{Fe_2(CO)_9}}$ goldish, decomposes at 100°C	$\underline{\underline{[Co(CO)_4]_2}}$ orange-red, m. p. 51°C
$\underline{\underline{[Fe(CO)_4]_3}}$ green, decomposes at 140°C	$\underline{\underline{[Co(CO)_3]_4}}$ black, solid, dec. at 60°C
$Ru(CO)_5$ colourless, m. p. −22°C	$\underline{\underline{[Rh(CO)_4]_2}}$ orange, dec. at 76°C
$\underline{\underline{Ru_2(CO)_9}}$ orange, sublimes	$\underline{\underline{[Rh(CO)_3]_x}}$ red, sublimes
$\underline{\underline{[Ru(CO)_4]_3}}$ green, crystalline	$\underline{\underline{Rh_4(CO)_{11}}}$ decomposes at about 200°C
$Os(CO)_5$ colourless, m. p. ca. −15°C	$\underline{[Ir(CO)_4]_2}$ yellow-green
$\underline{Os_2(CO)_9}$ yellow, m. p. 224°C (sublimes)	$\underline{[Ir(CO)_3]_x}$ yellow, dec. at 210°C

line is used for those having bridging CO groups, in addition.

Exchange Reactions of Carbonyls. All metal carbonyls exchange, more or less readily, molecules of carbon monoxide for other ligands. Such exchange reactions proceed especially readily under the action of light.

1. *Formation of Hydridocarbonyls (Carbonyl Hydrides).* When iron pentacarbonyl is heated with alkali, the following reaction takes place:

$$Fe(CO)_5 + 4NaOH \longrightarrow Na_2Fe(CO)_4 + 2H_2O + Na_2CO_3$$

The resulting compound $Na_2Fe(CO)_4$ is a salt-like compound in which sodium ions can be exchanged for other cations. For instance, the mercury derivative $HgFe(CO)_4$ has been prepared. When it is carefully acidified, an acid salt is first formed, this being followed by the formation of the acid, a **hydridocarbonyl**, $H_2Fe(CO)_4$ ($pK_1 = 4.4$; $pK_2 = 14$).

Similar carbonyl hydrides, or hydridocarbonyls, can be prepared by the reduction of dimeric carbonyls. For example, $[Mn(CO)_5]_2$

is reduced by hydrogen at 200°C:

$$[Mn(CO)_5]_2 + H_2 \longrightarrow 2HMn(CO)_5$$

Cobalt hydridocarbonyl, $HCo(CO)_4$, plays an important part in the Reppe oxo synthesis (see Volume I, page 174). In this synthesis, an olefin or acetylene adds H_2 and CO in the presence of a cobalt catalyst, forming an aldehyde. The hydrogen and carbon-monoxide carrier is, in fact, the transiently formed cobalt hydridocarbonyl:

$$CH_2=CH_2 + HCo(CO)_4 \longrightarrow CH_3-CH_2-Co(CO)_4$$

$$CH_3-CH_2-Co(CO)_4 + CO \longrightarrow CH_3-CH_2-\underset{\underset{O}{\|}}{C}-Co(CO)_4 \xrightarrow{H_2}$$

$$\longrightarrow CH_3-CH_2-\underset{\underset{O}{\|}}{C}-H + HCo(CO)_4$$

2. *Formation of Metal Alkylcarbonyls.* Hydridocarbonyls add across the olefinic and acetylenic π-bonds and form **metal alkylcarbonyls**, a typical reaction of which is the insertion of carbon monoxide into the metal-alkyl bond with the conversion of the latter into an acyl. Metal alkylcarbonyls (and arylcarbonyls) can be prepared from $NaMn(CO)_5$ and its analogues by the action either of CH_3I or its homologues (Hieber, Closson), or of $(C_6H_5)_3S^+ BF_4^-$ (A. N. Nesmeyanov, Yu. A. Chapovsky). The methyl derivatives are made through the interaction of diazomethane with a hydridocarbonyl. For example,

$$HMn(CO)_5 + CH_2=\overset{+}{N}=\overset{-}{N} \longrightarrow CH_3Mn(CO)_5 + N_2$$

Besides, taking advantage of the reversibility of the reactions of alkylcarbonyls with CO

$$RCo(CO)_4 + CO \rightleftarrows RCOCo(CO)_4$$

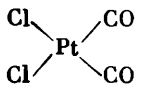
$$RMn(CO)_5 + CO \rightleftarrows RCOMn(CO)_5$$

it is possible, through the acylation of sodium salts of hydridocarbonyls, to prepare metal acylcarbonyls, which when heated give metal alkylcarbonyls (decarbonylation).

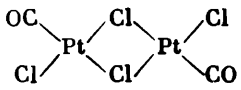
In metal alkylcarbonyls, the alkyl-transition metal bond, though not very stable, does nevertheless exist, and some compounds are resistant to temperatures up to about 100°C and higher. This is attributed to the effect of filling of the vacant *d*-levels of the metal (in this case, due to CO).

3. *Formation of Halogeno Metal Carbonyls* (*exchange of carbon monoxide for halogen*). Compounds of this type are known for the following metals: Cu, Au, Mn, Re, Fe, Ru, Os, Co, Rh, Ir, Pd, Pt. Such compounds, in which the metal is linked both to carbon mono-

xide and to halogen, can be prepared by two methods. The halides of copper and noble metals (if required, in the presence of a reducing agent) absorb carbon monoxide and form halogeno metal carbonyls (*metal carbonyl halides*). The following compounds have been obtained in this way: ClCuCO, ClAuCO, $I_2Ru(CO)_2$. Platinum when reacted with carbon monoxide and halogen forms



and



The second route—the action of a free halogen atom on metal carbonyls—is used to prepare the halogenocarbonyls of Mn, Fe, and Co. The reaction can be expressed schematically by the following equations:

$$Fe(CO)_5 + I_2 \longrightarrow I_2Fe(CO)_4 + CO$$

$$[Mn(CO)_5]_2 + Br_2 \longrightarrow 2BrMn(CO)_5$$

$$[Co(CO)_4]_2 + Cl_2 \longrightarrow 2ClCo(CO)_4$$

These halogenocarbonyls possess an ordinary exchangeable (though not ionic) halogen. Thus, with a Grignard reagent it is possible to obtain a metal alkylcarbonyl (or arylcarbonyl); with metal sodium-carbonyls, dimeric carbonyls are obtained:

$$ClMn(CO)_5 + NaMn(CO)_5 \longrightarrow [Mn(CO)_5]_2 + NaCl$$

The last reaction can also be accomplished with two different metal carbonyls:

$$ClRe(CO)_5 + NaMn(CO)_5 \longrightarrow (CO)_5Re-Mn(CO)_5 + NaCl$$

4. *Exchange of Carbon Monoxide for Ligands with a Free (Unshared) Electron Pair.* The most extensively studied class of reactions of metal carbonyls and also of halogeno metal carbonyls are substitution reactions in which one or more or, in rare cases, all carbon-monoxide groups are replaced by other ligands: amines (mainly, tertiary), phosphines, and PCl_3, arsines, stibines, cyano ions, isonitriles, etc., which may be illustrated by the following examples:

$$Ni(CO)_4 + 2C_5H_5N \longrightarrow Ni(CO)_2(NC_5H_5)_2 + 2CO$$

(Pyridine)

$$Cr(CO)_6 + 3C_5H_5N \longrightarrow Cr(CO)_3(NC_5H_5)_3 + 3CO$$

$$Cr(CO)_6 + 2P(C_6H_5)_3 \longrightarrow Cr(CO)_4[P(C_6H_5)_3]_2 + 2CO$$

$$ClMn(CO)_5 + 2C_5H_5N \longrightarrow ClMn(CO)_3(NC_5H_5)_2 + 2CO$$

5. *Exchange of Carbon Monoxide for Unsaturated Hydrocarbon Ligands.* Especially interesting to the organic chemist are substitution reactions in which carbon monoxide is replaced by unsaturated, particularly dienic and aromatic, hydrocarbons.

Olefins displace carbon monoxide from metal carbonyls if their π-bond is capable of undergoing nucleophilic attack or if there are two or more conjugated or non-conjugated double bonds conveniently arranged in space.

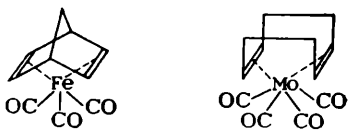
A typical example of reactions of the first kind is the action of tetrafluoroethylene and acrylonitrile on iron pentacarbonyl, which leads, respectively, to

$$(F_2C=CF_2)_2Fe(CO)_3 \qquad \text{and} \qquad (CH_2=CHCN)Fe(CO)_4$$

This clearly indicates that the olefin plays the role not only of a donor due to π-electrons but also of an acceptor for the *d*-electrons of the metal.

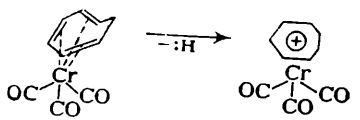
Butadiene with iron pentacarbonyl forms $C_4H_6Fe(CO)_3$.

Other examples of structures of the products resulting from the displacement of CO by means of dienes are as follows:



Cyclopentadiene displaces all carbon monoxide groups from $Ni(CO)_4$, giving $(C_5H_6)_2Ni$ with zerovalent nickel. This compound loses hydrogen and is readily converted into nickelocene, $(C_5H_5)_2Ni$ (page 133).

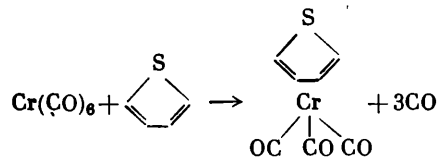
Cycloheptatriene displaces all the three CO groups in iron pentacarbonyl. In chromium hexacarbonyl it also displaces three carbonyl groups (Wilkinson), forming a complex which loses hydride ion abstracted, say, by the triphenylmethyl cation (Dauben, Honnen), and is converted into tropyliumtricarbonylchromium:

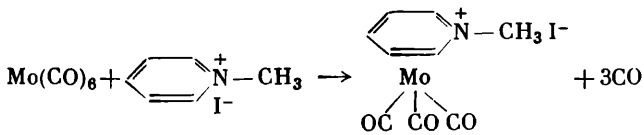


This is the first representative of **metal arenecarbonyls** that we encounter in the text. E. Fischer has found that metal arenecarbonyls can be prepared, in many cases, by the displacement of a part of CO from carbonyls through the action of an aromatic hydrocarbon on a metal carbonyl in an autoclave; in this reaction, the aromatic

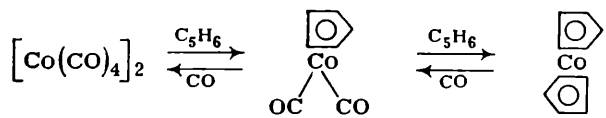
ring takes the place of all the three molecules of carbon monoxid

$$Cr(CO)_6 + C_6H_6 \longrightarrow C_6H_6Cr(CO)_3 + 3CO$$



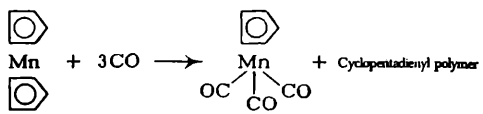


The role of an arene (i.e., of the aromatic ring) may be played by the cyclopentadienyl ion which has aromatic properties (see page 142 and Volume II, page 235). In some cases, the displacement of carbon monoxide by the cyclopentadienyl ion is effected directly by the action of cyclopentadiene on a metal carbonyl and may lead to the complete replacement of carbon monoxide with the formation of a sandwich-like compound—a metal dicyclopentadienyl:



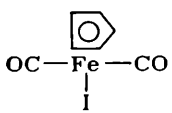
The hydrogen evolved from cyclopentadiene is consumed for the reduction of the excess cyclopentadiene.

In other cases, use is made of the reverse reaction. For instance, manganese cyclopentadienyltricarbonyl is prepared by the action of carbon monoxide on manganese dicyclopentadienyl:

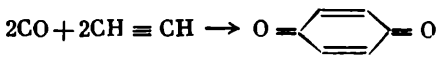


The properties of these, more or less aromatic, cyclopentadienyl metal carbonyls will be discussed in Chapter 13.

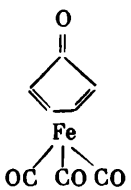
There also exist cyclopentadienylhalogeno carbonyls. One example is:



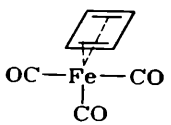
Acetylenes, just like polyenes, form complexes with carbonyls, which readily undergo further transformations, either with the participation of carbon monoxide or by way of cyclic polymerization. For example, $Fe(CO)_5$ and acetylene undergo the Reppe reaction in an aqueous-alcoholic solution, giving rise to the complexes $Fe \cdot C_{11}H_7O_5$ and $Fe \cdot C_8H_4O_4$. The complex $Fe \cdot C_{11}H_7O_5$ is decomposed by acids to form quinone. In this complex, two molecules of acetylene become attached to two molecules of carbon monoxide:



In the reaction leading to the formation of the complex $Fe \cdot C_8H_4O_4$, which is tricarbonylcyclopentadienoneiron



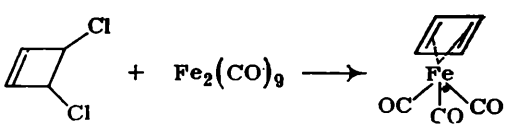
cyclopentadienone is apparently formed from two molecules of acetylene and one molecule of carbon monoxide. Finally, Orgel, using acetylene and iron pentacarbonyl, obtained a complex which was assigned the structure of tricarbonylcyclobutadieneiron



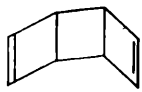
In addition to these complexes, the solution is found to contain the ethyl ester of acrylic acid (from acetylene, carbon monoxide and ethanol, the Reppe reaction, see Volume I, page 357) and hydroquinone.

Similar reactions are also known for substituted acetylenes. The compounds most readily undergoing this reaction are iron, cobalt, and nickel carbonyls. In certain cases, there is observed the formation of the products of trimerization of acetylenes to substituted benzenes (see Volume I, page 356).

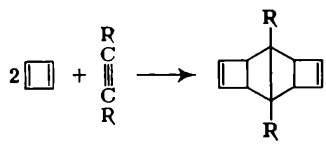
Pettit prepared tricarbonylcyclobutadieneiron also by the interaction between dichlorocyclobutene and iron nonacarbonyl:



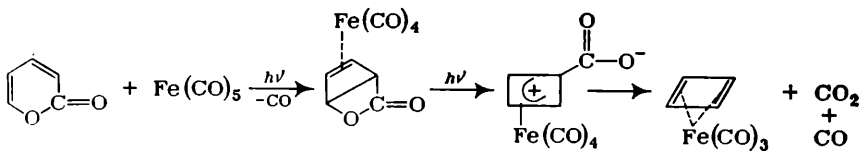
When the complex is oxidized by a cerium(IV) salt, it is decomposed and the departing cyclobutadiene dimerizes into a tricyclic unsaturated hydrocarbon:



and also forms more complex polymers. If an acetylene, RC≡CR, is introduced into the reaction at the moment when the complex is being decomposed, it unites with cyclobutadiene and a derivative of Dewar benzene is formed:



Tricarbonylcyclobutadieneiron has also been produced by another, unusual route: by means of a number of photochemical conversions of α-pyrone with iron carbonyl (Rosenblum and his co-workers, 1967):



According to the data obtained by Pettit, tricarbonylcyclobutadieneiron exhibits, like ferrocene, the ability to participate in a number of aromatic electrophilic substitutions. For example, it is acylated by the Friedel-Crafts reaction, mercurated, gives an aldehyde by the Vilsmeier reaction (with $C_6H_5NH{-}CHO$ and $POCl_3$), enters into the Mannich reaction (with CH_2O and HNR_2). Since we are not speaking here of a monocyclic carbocyclic compound, Hückel's rule ($4n + 2$) is evidently inapplicable.

B. Olefin π-Complexes of Transition Metals

The first coordination organometallic compound formed by an olefin and a transition metal was Zeise's salt (1827) prepared by the action of ethylene on potassium chloroplatinite:

$$K_2^+ [PtCl_4]^{2-} + C_2H_4 \longrightarrow K^+ [C_2H_4PtCl_3]^- + KCl$$

Using this classical compound as an example, it is convenient to get an insight into the type of bond between an olefin and a transition metal. Though even Werner stressed the analogy between this

reaction and the reaction of displacement of chlorine by ammonia into the outer sphere

$$K_2^+[PtCl_4]^{2-} + NH_3 \longrightarrow K^+[NH_3PtCl_3]^- + KCl$$

the analogy between the behaviour of ammonia, which adds to the metal via its free pair of electrons, and that of the olefin is however incomplete.

For example, olefins, such as $CF_2=CF_2$, with a "depleted" π-bond become attached to a metal not worse than ethylene. Thus, the olefin-metal bond must have not only a donor but also an acceptor character. Developing the ideas first put forth by Dewar, Chatt and Duncanson came to the concept schematically shown in Fig. 12.13.

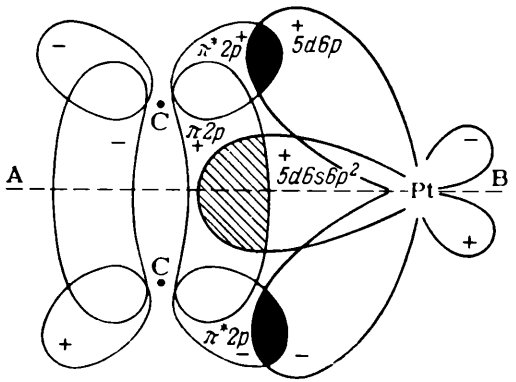


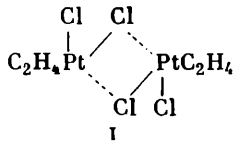
Fig. 12.13.

Diagram showing the overlap of the orbitals of platinum and ethylene in the formation of a π-complex of Zeise's salt type.

An olefin unites with platinum in a dual way: a bond of the σ-type (the hatched area in the figure) is formed as a result of the overlap of the π-orbital of the olefin with the $5d6s6p^2$ orbital of platinum. Besides, the olefin and the metal are bound additionally by a bond of the π-type since the metal donates the electrons of the $5d6p$ orbital to the antibonding π*-orbitals of the olefin (the black overlap regions). The structure of the anion of this square complex of divalent platinum (dsp^2-hybridization in the language of localized pairs) is schematically shown in Fig. 12.14.

Hence, for this additional (on the part of the metal) dative bond of the π-type to be formed, there must be electrons on the *d*-orbitals of the metal. This is the reason why olefinic π-complexes can be formed only by the elements at the ends of the long periods (Ni, Pd, Pt, Cu, Ag, Au) with filled or almost filled *d*-levels.

Apart from complexes of Zeise's salt type, platinum with olefins also forms neutral molecules (and not anions) of the type I:



I

which are dimeric due to chlorine bridges.

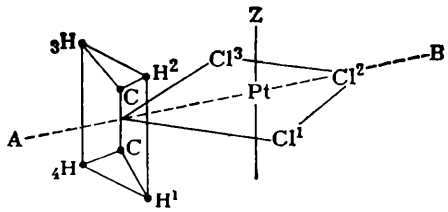


Fig. 12.14.

Diagrammatic representation of the structure of the anion of a π-complex of platinum and ethylene (Zeise's salt).

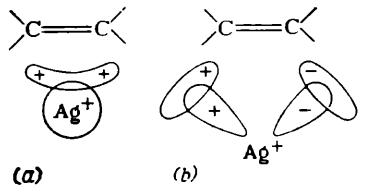


Fig. 12.15.

Diagram showing the overlap of the orbitals of the silver ion and an olefin in a π-complex:
a and *b*—different types of bond.

Kharasch was the first to obtain analogous palladium-olefin complexes with Pd(II) through the displacement of the nitrile ligand by an olefin:

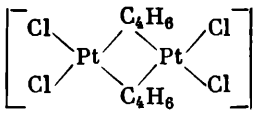
$$(C_6H_5CN)_2PdCl_2 + \text{Olefin} \longrightarrow \left[\begin{matrix}\text{Olefin}\\ \\ \text{Olefin}\end{matrix}\!\!>\!\!PdCl_2\right]_2 + 2C_6H_5CN$$

Further examples of π-complexes of this type are complexes of the silver ion (Fig. 12.15) identified by Winstein and Lucas in studying the law of distribution of an olefin between the hydrocarbon layer and the aqueous solution of silver nitrate, a considerable amount of olefin being passed into the aqueous solution. The bonds of the σ-type formed by the *s*-orbital of silver and the π-orbital of the olefin are shown in Fig. 12.15*a*, and the dative bond of Ag^+ to the antibonding π*-orbitals of the olefin is pictured in Fig. 12.15*b*. As is always the case, the plus and minus signs signify the signs of the function regions and not the charge signs.

Polyenes, especially those with conjugated bonds, form π-complexes with transition metals even more readily than do olefins. In this case, a diene occupies two coordination sites and the direct interaction of a diene, say, with K_2PtCl_4, occurs as follows:

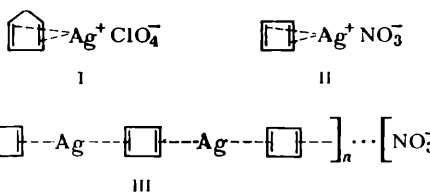
$$2K_2PtCl_4 + CH_2{=}CH{-}CH{=}CH_2 \longrightarrow K_2\left[\begin{matrix}Cl & & Cl\\ ClPt-C_4H_6-& & PtCl\\ Cl & & Cl\end{matrix}\right]^{2-} + 2KCl$$

On further interaction of butadiene, the anion converts into a neutral greenish-brown dimer (A. D. Gelman):



When butadiene is reacted with dimer I (see page 119), an isomer of the dimeric molecule given above is formed, which is a dark-red substance with chlorine bridges instead of butadiene bridges. Dimeric complexes (similar to olefin complexes) in which the diene occupies two coordination sites, are also formed by Pd(II) with dienes.

The argentous ion with polyenes forms crystalline π-complexes, say, complex I with cyclopentadiene, complex II or, possibly, a complex of polymeric structure III with cyclobutadiene:



and also complexes with 1,5-cyclooctadiene and cyclooctatetraene.

Dienes add to the halides of univalent copper and give products of diene-CuX addition in the ratio of 1 : 1 or 1 : 2. This is utilized for separation of dienes from olefins. Thus, with CuCl and CuBr butadiene forms complexes of the 1 : 2 composition and 1,5-cyclooctadiene forms 1 : 1 complexes; cyclooctatetraene gives 1 : 2 complexes with CuCl, and 1 : 1 complexes with CuBr.

Probably, only nickel gives complexes in which a polyene is the only ligand. An example is a very labile air-oxidized cyclododecatrienenickel, $C_{12}H_{18}Ni$

a dark-red substance which crystallizes in needles. It is prepared by the Wilke reaction, by the action of *trans-trans-trans*-cyclododecatriene on nickel acetylacetonate in the presence of a reducing agent, $(C_2H_5)_2AlOC_2H_5$.

As can be seen, the nickel in this compound is formally zerovalent. Cyclododecatriene adds six π-electrons to the outer electron shell of nickel, thereby making 16 electrons in total. This explains why

this compound is still capable of adding a molecule of triphenylphosphine, supplementing the outer shell with a free electron pair up to 18 electrons (a stable inert-gas configuration), i.e., up to 36 electrons in total—the number of electrons in krypton (the Sidgwick effective atomic number rule). From this remarkable compound other polyenes displace cyclododecatriene and form, in their turn, complexes with nickel, say, 1,5-cyclooctadiene gives $Ni(C_8H_{12})_2$, and cyclooctatetraene affords a polymeric complex, $Ni(C_8H_8)$. A particularly interesting substance is the product obtained in the reaction with butadiene: an isomer of cyclododecatrienenickel of the same composition, $C_{12}H_{18}Ni$, is formed, but with a ligand which is an open chain of atoms. This has been established by the hydrogenation of the compound, which yields *n*-dodecane (in the case of cyclododecatriene, hydrogenation, of course, yields cyclododecane). Thus, three molecules of butadiene are linearly added to one another, which may be represented schematically as follows:

$$CH_2=CH-CH=CH_2+CH_2=CH-CH=CH_2+CH_2=CH-CH=CH_2 \longrightarrow$$

$$\longrightarrow CH_2=CH-\dot{C}H-CH_2-CH_2-\dot{C}H-\dot{C}H-CH_2-CH_2-\dot{C}H-CH=CH_2 \longrightarrow$$

$$\longrightarrow CH_2=CH-\dot{C}H-CH_2-CH_2-CH=CH-CH_2-CH_2-\dot{C}H-CH=CH_2$$

Such a biradical of the allyl type is capable of donating exactly 8 electrons needed to increase the number of electrons in the outer sphere of nickel to 18 electrons (6 electrons coming from the three π-bonds and 2 electrons from two radicals of the allyl type), so that structure I results, but since the electrons are delocalized within the allylic system this structure is better represented as II:

I

II

Here we encounter, for the first time, the so-called π-allyl ligand of organometallic complexes.

If we recall that nickel cyanide and ammine were used by Reppe (see Volume I, page 356) as catalysts for the polymerization of acetylene to cyclooctatetraene, cyclodecapentaene and benzene, it will be clear that these reactions proceeded via the complex-formation of acetylene with nickel.

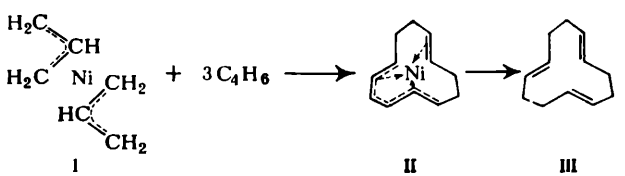
Although nickel is extremely active in polymerization reactions of this type, it is not the only metal that causes such conversions. For example, Ziegler polymerization catalysts (triethylaluminium

mixed with $TiCl_4$ or $TiCl_3$) also trimerize butadiene to cyclododecatriene. This is an ordinary method of synthesis of cyclododecatriene, which proceeds (according to Wilke) through the following three stages: (a) the formation of a butadiene π-complex with a transition metal; (b) the formation of carbon-carbon bonds in the three butadiene molecules oriented around the central metal atom; (c) the displacement of the thus formed cyclododecatriene by butadiene.

We have already encountered (see Volume III, page 22) the trimerization of acetylene to benzene and of substituted acetylenes to substituted benzenes, which takes place by means of the various transition metal complexes. Such trimerization reactions will also be discussed in the following section. It should also be recalled that the linear dimerization and linear trimerization of acetylene to vinylacetylene and divinylacetylene are conducted, according to Nieuwland (see Volume I, page 355) in a solution of cuprous chloride in liquid ammonia and ammonium chloride. Thus, transition metal complexes serve as excellent catalysts for unusual syntheses, the possibilities of which are far from being exhausted and which are being intensively studied at present.

Having taken into consideration the donor-acceptor character of transition metal-olefin bonds, we begin to understand that metal carbonyls, which fill its electron shell owing to carbon-monoxide groups (this also refers to carbonyls of those metals which are far away from the ends of the long periods, such as Fe, Mn, Cr, V) form the olefin-metal carbonyls described above but do not give purely olefin derivatives.

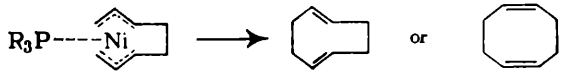
Brief mention should be made here of the π-allyl derivatives of metals, a rather complex representative of which, the nickel compound II, has been considered above. The simplest π-allyl derivatives of transition metals are formed by the action of allylmagnesium halide or allyllithium on chlorides of transition metals. For instance, using allylmagnesium chloride and divalent nickel, Wilke prepared bis-π-allylnickel I, a substance which is volatile even with ether vapours. Butadiene displaces from it the allyl radicals which couple into diallyl and is itself trimerized, via complex II, to cyclododecatriene III:



I II III

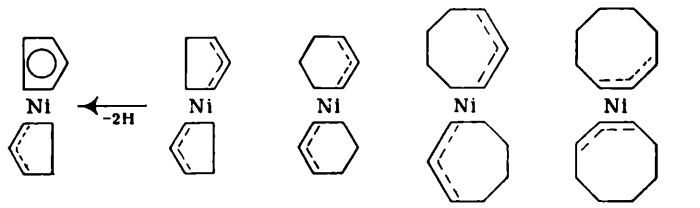
But if butadiene (2 moles) is allowed to react in the presence of compounds of the type R_3P, cyclooctadiene V is formed via the

intermediate π-allyl complex IV:

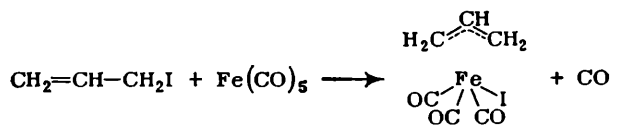


IV V

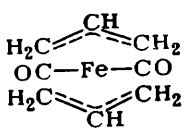
Below are also given the π-allyl complexes of nickel with more complex cyclic allylic systems (enclosed in parentheses are the temperatures above which these complexes are unstable):



The π-allyl (and also allyl) complexes with other ligands have been investigated more extensively. The following examples provide information on these complexes and on methods of their preparation, say, the preparation of π-allyltricarbonyliron iodide (Murdoch):



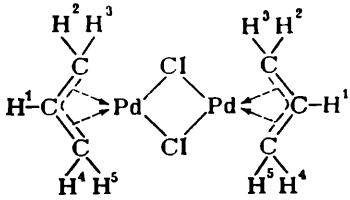
When this compound is reduced with sodium amalgam and is further treated with an additional amount of allyl iodide, bis-π-allyldicarbonyliron is obtained (A. N. Nesmeyanov, I. I. Kritskaya):



Nickel as well as iron π-allyl complexes decompose with the formation of diallyl or "di(allyl)" ketones.

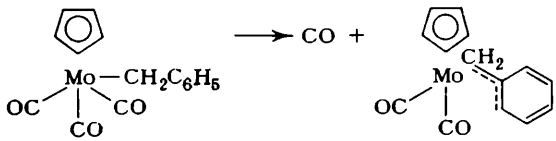
An attempt to obtain allylpalladium chloride, $CH_2=CH-CH_2-PdCl$ (the so-called σ-allylpalladium chloride) by the action of allylmagnesium chloride on palladium chloride results in the formation not of the expected product but of dimeric π-allylpalladium chloride

in which the allyl radical is linked to palladium via a π-bond and in such a manner that, in addition to the two π-electrons of the π-bond, the unpaired but delocalized *p*-electron of the allyl radical is also involved. Both terminal methylene groups of the allyl are found to be absolutely identical (three kinds of protons have been detected, whose NMR spectrum intensities are in the ratio $2(H^2H^4):2(H^3H^5):1(H^1)$, which corresponds to the following structure:



Such types of π-allyl compounds are widespread among the transition metals, but, along with the allyl, these compounds contain other ligands as well.

The analogues of π-allyl complexes are π-benzyl complexes. A complex of this kind was first produced by King by irradiation of σ-benzyl-π-cyclopentadienyltricarbonylmolybdenum:



The starting compound accepted from the ligand $5 + 2 \times 3 + 1 = 12$ electrons on the orbitals of the metal, which completed the outer electron shell of molybdenum to the number corresponding to the effective atomic number of xenon (σ-benzyl donates one electron). Upon irradiation the benzyl radical, due to one of the π-pairs of benzene, displaces one carbon monoxide molecule and gives three electrons, one radical and two π-benzene electrons, and becomes a π-benzyl ligand, destroying its benzenoid character to a certain extent.

C. Metalloarenes

Since benzene possesses some of the properties of a triene, it is not so much surprising as unexpected that there exist organometallic π-complexes of transition metals with benzene and other aromatic compounds. We have already seen that aromatic compounds are capable of displacing three carbon-monoxide groups and replace them with one aromatic ring, leaving the CO ligands bound to a

zerovalent metal. In this way, there are obtained **metal arenecarbonyls**; data on selected metalloarenes are presented in Table 12.4.

TABLE 12.4. Metal Arenecarbonyls

Formula	m. p., °C	Colour
$C_6H_6Cr(CO)_3$	161-163	Yellow
$C_{10}H_8Cr(CO)_3$	150 (dec.)	Yellow
$ClC_6H_5Cr(CO)_3$	102-103	Yellow
$NH_2C_6H_5Cr(CO)_3$	173-175 (dec.)	Yellow
$C_6H_6Mo(CO)_3$	120-125	Green-yellow
$C_6H_6W(CO)_3$	140-145	Yellow
$1,3,5\text{-}C_6H_3(CH_3)_3\overset{+}{M}n(CO)_3$	—	Yellow

However, bis-arene compounds of the sandwich type, in which two aromatic rings are linked to the atom (or cation) of a transition metal (Table 12.5) are produced in a different way.

TABLE 12.5. Bis-Arenes of Transition Metals

Formula	m. p., °C	Colour	μ_{eff}
$(C_6H_6)_2V$	277-278	Red-brown	1.73
$(C_6H_6)_2Cr^+$	—	Yellow	1.73
$(C_6H_6)_2Cr^0$	282-284	Dark-brown	0
$(C_6H_6)_2Mo$	115 (dec.)	Green	0
$(C_6H_6)_2W$	110 (dec.)	Yellow-green	0
$[C_6(CH_3)_6]_2Mn^+$	—	Pink	0
$(C_6H_6)_2Re^+$	—	Red-brown	0
$(C_6H_6)_2Fe^{2+}$	—	Yellow	0
$[1,3,5\text{-}C_6H_3(CH_3)_3]_2Ru^+$	—	Red-brown	0
$[1,3,5\text{-}C_6H_3(CH_3)_3]_2Os^{2+}$	—	Yellow	—
$[1,3,5\text{-}C_6H_3(CH_3)_3]_2Co^{3+}$	—	Red-brown	—
$[1,3,5\text{-}C_6H_3(CH_3)_3]_2Rh^{3+}$	—	Light-brown	—
$[1,3,5\text{-}C_6H_3(CH_3)_3]_2Ir^{3+}$	—	Yellow-brown	—

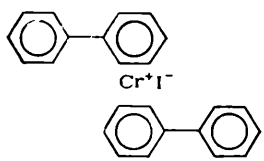
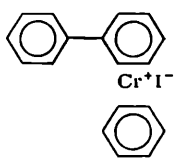
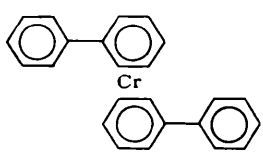
The simplest method is due to E. Fischer. A benzene solution (or, in general, a solution in an aromatic compound) or a suspension of a halide of a transition metal is heated with aluminium chloride and aluminium dust, the latter being used as a catalyst*. This leads

* Compare with the preparation of metal carbonyls by the method developed by A. N. Nesmeyanov, K. A. Kocheshkov, and K. N. Anisimov (page 110).

to the formation of metal bis-benzene (a metal bis-arene, in general) with a zerovalent metal which loses, more or less readily, an electron, being oxidized, often in air, to bis-arenemetal cation.

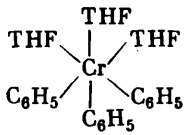
It should be noted that the first bis-arenechromium compounds were prepared by Hein as far back as 1919 by the action of a Grignard reagent, C_6H_5MgBr, on $CrCl_3$. The first sandwich structure, ferrocene (page 129), however, was reported only in 1952. In 1919 Hein mistook the compounds prepared by him for ordinary organometallic compounds, namely for the phenyl derivatives of chromium (see Table 12.6).

TABLE 12.6

	Hein structures (1919)	Structures suggested by Onsager (1954)
I	$(C_6H_5)_4Cr^+I^-$	
II	$(C_6H_5)_3Cr^+I^-$	
III	$(C_6H_5)_4Cr$	

Naturally, the structures shown in Table 12.6 cannot be distinguished on the basis of the data of analysis: Hein and Onsager structures I are isomeric to each other just as structures III, and only structures II differ from each other by one hydrogen atom. The preparation of dibenzenechromium and a series of its homologues by Fischer and their investigation provided a conclusive clue to the solution of the problem. It is interesting to note that Zeiss, who studied the Hein structures and experimentally established their identity to benzene-

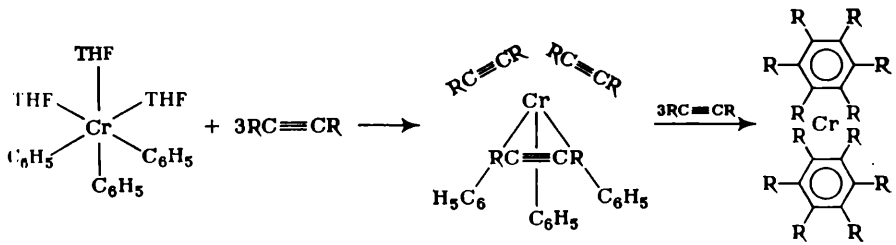
biphenylchromium iodide and bis-biphenylchromium iodide, succeeded also in preparing the phenyl derivatives of chromium by the Grignard reaction in a tetrahydrofuran (THF) solution. In this case, three THF molecules become incorporated into the complex as ligands and stabilize it:



Water decomposes this red substance, converting it into the green cation $Cr^{3+}(OH_2)_6$, and mercuric chloride eliminates phenyl groups forming C_6H_5HgCl. If the reaction is carried out in ether, the stability of the etherate is even lower (ether is a poorer donor than THF), and it spontaneously (and the complex with THF does so on heating) rearranges into a black compound, the hydrolysis of which yields a mixture of bis-arenechromiums:

$$(C_6H_5)_3Cr(THF)_3 \xrightarrow{\text{heat; then } H_2O} \begin{matrix} C_6H_6 \\ Cr \\ C_6H_6 \end{matrix} + \begin{matrix} C_6H_6 \\ Cr \\ C_6H_5-C_6H_5 \end{matrix}$$

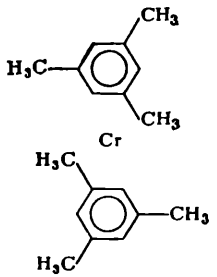
Extremely interesting is also the behaviour of triphenylchromium towards acetylenes, discovered by Zeiss. Acetylenes displace both tetrahydrofuran and phenyl groups and undergo cyclization into substituted benzenes, forming bis-arenechromium:

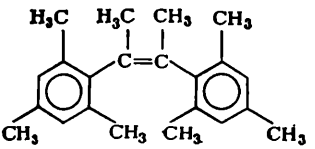


In this way, for example, dimethylacetylene yields bis-hexamethylbenzenechromium.

Thus, Zeiss discovered the second route for the synthesis of bis-arenechromiums. It is interesting to note that phenyl groups participate in the reaction and, condensing with two molecules of dimethylacetylene, give a certain amount of 1,2,3,4-tetramethylnaphthalene. If, instead of triphenylchromium, use is made of trimesitylchromium in tetrahydrofuran, then, along with bis-arene I, as a result of addition of mesityl to dimethylacetylene followed by hydrolysis

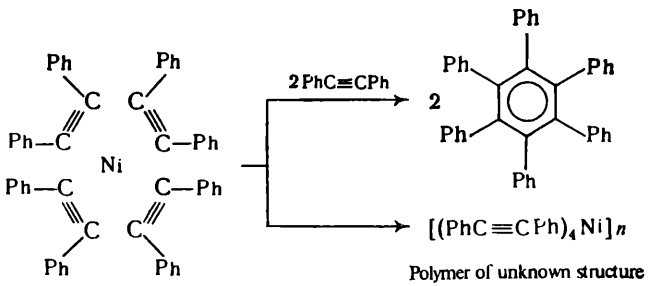
there is formed 2,3-dimesityl-2-butene (II):





II

Salts of nickel and cobalt in tetrahydrofuran with a Grignard reagent also form unstable diarylnickel tetrahydrofuranates and cobalt tetrahydrofuranates, respectively. More stable are the dimesityl derivatives of these metals. Diphenylacetylene (Ph = phenyl) reacts over a nickel compound as follows:



In this case, just as in general, bis-arenenickel cannot be isolated. Diphenylcobalt and tetrahydrofuran are evidently capable of cyclizing unlimited amounts of acetylenes catalytically into benzene derivatives, but no arenes have been isolated either for nickel or for cobalt.

In a few cases, there have been obtained bis-arenes of transition metals and a rather large number of arenecarbonyls not only with hydrocarbon arenes but also with heterocyclic arenes (e.g., with thiophen) or with substituted benzenes—phenylacetic acid, aniline and its derivatives, chlorobenzene, etc. But the presence of strong electron-attracting groups, such as, for example, NO_2, $-C\overset{O}{\underset{H}{<}}$, CN, and even COOH, does not allow the benzene ring to form bis-arenes or arenecarbonyls. On the contrary, arenes and arenecarbonyls containing alkyl substituents in the aromatic ring are more stable than benzene ones.

D. Metallocenes

In 1951 Pauson, a young chemist from Sheffield, made a surprising discovery: in an attempt to prepare dicyclopentadienyl by the action of ferric chloride on a Grignard reagent from cyclopentadiene

he isolated dicyclopentadienyliron which is exceedingly stable, even at temperatures up to 400°C, distils with steam and is decomposed neither by acids nor by alkalis. (Alkyl and aryl derivatives of iron have not yet been obtained and, of course, if they do exist at low temperatures they are extremely unstable.) Shortly after this discovery, Woodward, Rosenblum and Wilkinson established, by X-ray analysis, the unusual "sandwich" structure of dicyclopentadienyliron. At a later time, there was discovered the first aromatic substitution reaction for iron dicyclopentadienyl involving the replacement of hydrogen—the Friedel-Crafts acylation reaction. Woodward and Wilkinson proposed the name **ferrocene** for the new aromatic system.

These discoveries laid the foundation of a new branch of chemistry—the chemistry of sandwich-like cyclopentadienyl **metallocenes** and gave an impetus to the study, especially in the case of ferrocene, of their aromaticity and also played a decisive role in the development of the chemistry of sandwich-like arenes.

Most of the transition metals form sandwich compounds, **cenes**, with two cyclopentadienyl rings, and uranium and the rare-earth elements give such compounds with three cyclopentadienyl rings. On the basis of the physical and chemical properties it is believed that tricyclopentadienyl-rare-earth metals (among tricyclopentadienyl metals) and dicyclopentadienylmanganese and dicyclopentadienylmagnesium (among dicyclopentadienyl metals) have ionic structures, though the last two compounds, just as all other dicyclopentadienyl metals, possess a sandwich structure. In other metallocenes the ring-metal bond is similar to that in ferrocene. An idea of the ring-metal linkage can be gained from a correlation diagram of energy levels (molecular orbital method) given in Fig. 12.16.

Here the energy levels of the π-electrons of the aromatic sextets of cyclopentadienyl anions are split into three unequal levels a, e_1, and e_2 (see Volume III, page 16, where the MO levels for benzene are described). These orbitals of the ligand combine with the atomic orbitals of the metal. The greatest contribution is made by the combination of the orbitals of the rings with the energetically comparable $3d\pi$-orbitals (i.e., $3dxy$, etc.) of the metal. Hence, the linkage between the metal and cyclopentadienyl rings may be roughly described

as the only bond of σ-character with each ring. Just as in the preceding diagrams, the filled circles represent electrons that have occupied the given orbitals, and the half-filled circles stand for electrons which may be either present or absent in this or that metallocene or its cation; the unfilled circles are vacant orbitals. Thus, in the ion $Ti(C_5H_5)_2^{2+}$ the half-filled circles are all vacant and should be unfilled. In ferrocene, the 2σ′- and 1δ′-orbitals are occupied and the circles must be filled. The ion $Co(C_5H_5)_2^+$ is isoelectronic with $Fe(C_5H_5)_2$. It is exactly the cobalticenium ion and ferrocene (the most stable among the metallocenes) that have the full Sidgwick effective number, i.e., the number of electrons of the nearest inert gas, krypton: 36 in total, and 18 electrons in the outer shell.

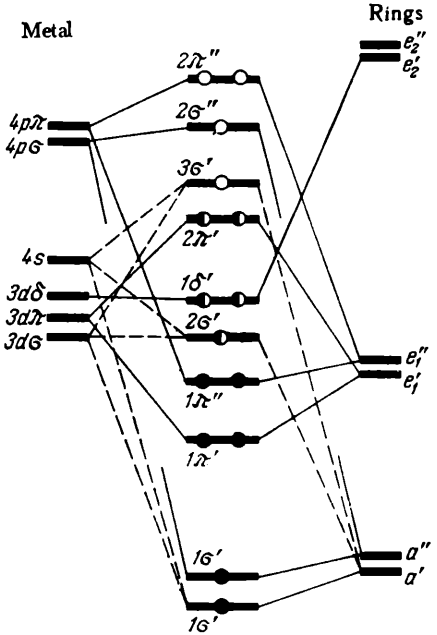


Fig. 12.16.
Energy-level diagrams for ferrocene and analogous compounds.

Below are given a number of well-known metallocenes (the number of unpaired electrons determined by the presence and degree of paramagnetism is enclosed in parentheses):

$(C_5H_5)_2Ti$ (0);	$(C_5H_5)_2V$ (3);
$(C_5H_5)_2Cr$ (2);	$(C_5H_5)_2Mn$ (5)
$(C_5H_5)_2Co$ (1);	$(C_5H_5)_2Ni$ (2);
$(C_5H_5)_2Ru$ (0);	$(C_5H_5)_2Os$ (0)

The leading investigators of a large variety of metallocenes are E. O. Fischer and G. Wilkinson. They have effected the synthesis of most metallocenes and studied their physical properties and structure.

All dicyclopentadienyl compounds of the elements of the first long period have, like ferrocene, a melting point of about 173°C and form crystals isomorphic with it. An exception is the ionic compound $(C_5H_5)_2Mn$. Ruthenocene and osmocene are chemically very similar to ferrocene. Many of the elements form dicyclopentadienyl halides, which are compounds with other anionoid groups, and also hydrides. Some representatives of these compounds are listed in Table 12.7.

They are all formed by the action of C_5H_5Na on salts of the corresponding metals, sometimes followed by reduction.

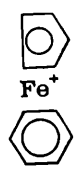
TABLE 12.7

	IV	V	VI	VII
4	$(C_5H_5)_2TiX$ $(C_5H_5)_2TiX_2$	$(C_5H_5)_2VX_3$		
5	$(C_5H_5)_2ZrCl_2$	$(C_5H_5)_2NbX_3$	$(C_5H_5)_2MoX_2$ $(C_5H_5)_2MoH_2$	
6		$(C_5H_5)_2TaX_3$	$(C_5H_5)_2WH_2$	$(C_5H_5)_2ReH$

$(C_5H_5)_3UX$

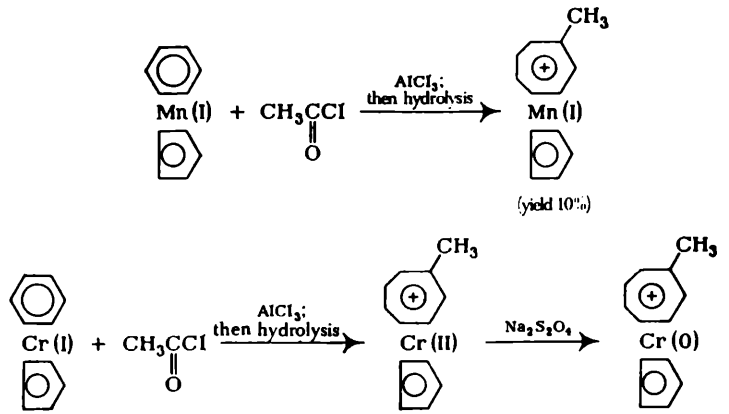
As has been said, ferrocene and cobaltocene are oxidized, the latter especially readily, losing an electron and being converted into the ferricenium and cobalticenium ions, respectively. In contrast to the starting neutral compounds and like the substances mentioned above, these cations are not able to undergo substitution reactions in cyclopentadienyl rings, say, aromatic electrophilic substitution reactions.

The stability of the cyclopentadienyl-metal bond varies from compound to compound: it is the most stable in ferrocene, ruthenocene and osmocene, and also in the cobalticenium ion. According to the data obtained by A. N. Nesmeyanov and E. G. Perevalova, ferrocene is hydrogenated over Raney nickel by hydrogen only at 300°C and under a pressure of about 300 kg/cm^2, forming cyclopentane. A. N. Nesmeyanov and N. A. Volkenau have found that one of the rings of ferrocene can be replaced by benzene or other aromatic systems by boiling in the presence of aluminium chloride. With benzene the reaction gives the cation



which can be isolated in the form of salts with the anions BF_4^-, $(C_6H_5)_4B^-$ or PF_6^-. This cation is extremely stable to oxidation and reduction. It is a representative of the yet small class of **metallocenearenes** which will not be considered in detail here. We shall only point out that compounds of this type, which are prepared by the action of an aromatic hydrocarbon on cyclopentadienyl metal

carbonyls, have been largely studied by E. O. Fischer. The most remarkable conversions of benzenecyclopentadienyl metals (Cr and Mn) are reactions under the conditions of the Friedel-Crafts acylation, leading to the conversion of the benzene ligand into the methylpropylium ligand:



Enclosed in parentheses are the formal valencies of the metals in the compounds given.

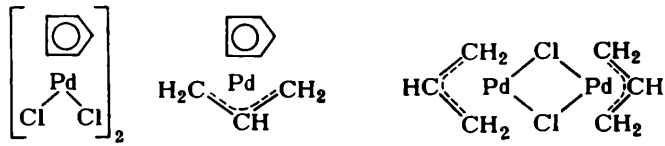
In contrast to stable ferrocene, some cyclopentadienyl derivatives of titanium, say, $C_5H_5Ti(OC_2H_5)_3$, lose cyclopentadiene even under the influence of ethanol at 20°C, as a result of which the compound is converted into ethylorthotitanate, $(C_2H_5O)_4Ti$. The cleavage of the Ti—C_5H_5 bond under the action of ethanol at room temperature occurs readily in the case of $(C_5H_5)_2Ti(OCOCH_3)_2$. The elimination of one of the cyclopentadienyl rings from $(C_5H_5)_2TiCl_2$ (true, only to an insignificant extent) is observed also on prolonged boiling of an alcoholic solution of this compound (A. N. Nesmeyanov, O. V. Nogina). But the ferricenium ion is more easily destroyed than ferrocene, with a partial elimination of cyclopentadienyl rings (e.g., by alkali), being converted into ferrocene, with liberation of metallic iron and an organic polymer.

In many cases, cyclopentadienyl half-sandwich compounds are known, which contain one cyclopentadienyl ring π-bonded to the metal and other ligands. One such compound has already been encountered in the case of $C_5H_5Ti(OC_2H_5)_3$. Its chlorine analogue can be prepared by the following reaction:

$$(C_5H_5)_2TiCl_2 + 3Cl_2 \xrightarrow{h\nu} C_5H_5TiCl_3 + C_5H_5Cl_5$$

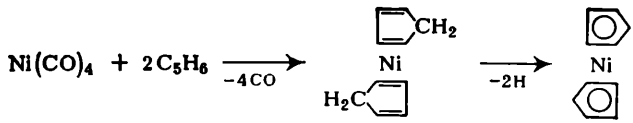
Titanium seems here to be tetravalent in total. Bis-(cyclopentadienyl)-titanium and bis-(cyclopentadienyl)-titanium(III) chloride are prepared by the reduction of compounds of tetravalent titanium

A further example of a monocyclopentadienyl half-sandwich is a derivative of divalent palladium I, which can be converted by the action of an allylmagnesium chloride into π-cyclopentadienyl-π-allylpalladium II. In this compound, the π-allyl ligand is held more firmly than the π-cyclopentadienyl ligand. For instance, the action of mercuric chloride eliminates the cyclopentadienyl ring (in the form of C_5H_5HgCl), leaving a rather stable compound III (A. N. Nesmeyanov, S. P. Gubin, A. Z. Rubezhov):

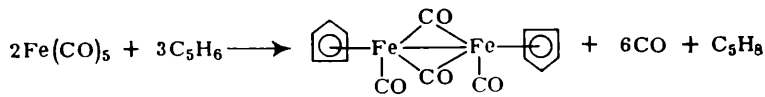


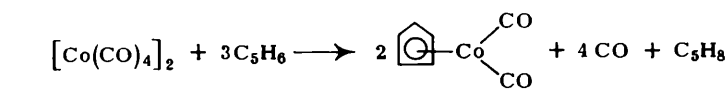
I II III

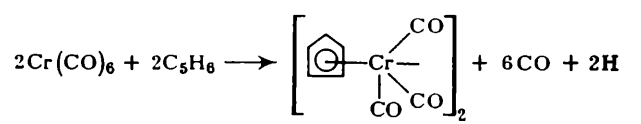
In the majority of cases, however, such monocyclopentadienyl derivatives are known to have ligands of the carbon-monoxide type. They are most simply prepared by the action of cyclopentadiene on a metal carbonyl (E. O. Fischer). In the case of nickel, in which all carbon monoxide is replaced, we can single out the intermediate stage—the formation of nickel dicyclopentadiene, which under more vigorous conditions loses hydrogen and turns into nickelocene:



A similar course of the reaction may also be assumed for other metal carbonyls, but in such a case only one cyclopentadiene enters into the displacement reaction per metal atom:

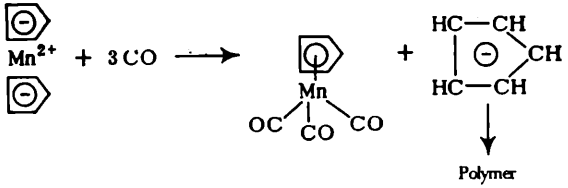




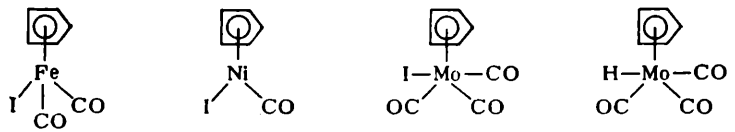


An especially interesting compound is highly aromatic **cyclopentadienyltricarbonylmanganese** or **cymanthrene**, which has to be

prepared by the reverse reaction—the action of carbon monoxide on dicyclopentadienylmanganese (an ionic compound, as has already been said):



Mixed cyclopentadienylhalogeno carbonyls and hydrides of transition metals are also known. We shall only give their formulas:



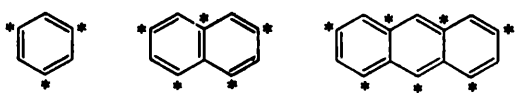
Analogous compounds are formed by tungsten (Wilkinson). Apart from the remarkable ability of transition metal complexes to crosslink olefinic molecules with one another and with carbon monoxide, perhaps, of the utmost interest to the organic chemist in the entire field of the organic chemistry of transition metals is the unusually sharply pronounced aromatic properties of ferrocene and its ruthenium and osmium analogues (ruthenocene and osmocene) and cyclopentadienyltricarbonylmanganese. These purely organic reactions are discussed in Chapter 13.

Chapter 13

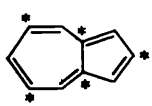
Non-Benzenoid Aromatic Systems

In the isocyclic aromatic systems considered so far, including fused-ring (condensed) systems, the benzene ring has invariably served as the aromatic ring.

Benzene contains six equally shared π-electrons. It belongs to the so-called **alternant** aromatic systems, in which, if we mentally fix the electrons of the π-bonds one on each carbon atom, their spins will alternate. Alternant systems (or alternants) have the property that their carbon atoms, of which the aromatic system is composed, fall into two sets distinguished as starred and unstarred:



No atom of one set is adjacent to another of the same set, i.e., the atoms of the two different sets alternate regularly. **Non-alternant** aromatic systems contain odd-membered rings; they will be considered at a later time. An example of non-alternant hydrocarbons is azulene, an isomer of naphthalene,



For non-alternant hydrocarbons, the atoms cannot be divided into two sets, starred and unstarred, with no two members of the same set being bonded together.

The sharply pronounced alternation of the electrophilicity and nucleophilicity of the carbon atoms in benzene is not characteristic of non-alternant aromatic systems.

Quantum-mechanical calculation based on the molecular orbital method (in the Hückel approximation) leads to the conclusion that systems with a sharply decreased energy (in the ground state of the molecule) will be all unsaturated cyclic compounds with conjugated π-bonds if the number of π-electrons in them is equal to $4n + 2$, where n is any integer (this conclusion applies only to monocyclic systems). Thus, the "aromatic sextet" of electrons in benzene ($4 \times 1 + 2 = 6$) is a special case, though the most important one. Since the approach of the molecular orbital method to the consideration of the molecule is the same as the quantum-mechanical treatment of the atom, the stable aromatic sextet of electrons and all $4n + 2$ groupings may be compared with the stable closed electron octets in atoms (and ions) of the elements at the top of the periodic system (B-Ne). Thus, at $n = 0, 1, 2, 3, 4$, stable electron groupings will, respectively, contain 2, 6, 10, 14, 18 p-electrons. Owing to the low energy systems containing this number of electrons in π-bonds are more stable than other unsaturated systems. The double bonds in them are more difficultly broken; in other words, these systems exhibit a decreased tendency towards additions (as has been shown for benzenoid aromatic systems), and therefore substitution reactions are the main reactions for them.

In all aromatic systems, there is a closed ring, which differentiates them from open conjugated polymethine systems:

$$X-CH=CH-CH=CH-\cdots X$$

In isocyclic aromatic systems, either alternant or non-alternant, all the atoms of the aromatic ring are in a state of sp^2 hybridization (see Volume I, page 326), and π-electrons are free to move along the periphery of the ring, just as a current flows along an infinitely conducting metal. Such a behaviour of electrons confers special optical and diamagnetic properties on aromatic systems.

13.1. Diamagnetic Properties of Aromatic Systems

When a system of atoms is introduced into a magnetic field, each electron acquires a small additional momentum and, as a consequence, an additional induced magnetic moment which is opposite to the direction of the applied field and weakens it. All this is quite analogous to the behaviour of a solenoid in which a current is flowing and which is placed in a magnetic field. The solenoid becomes perpendicular to the direction of the field and creates a field of opposite direction, proportional to the coil area of the solenoid. The atoms however are held within the molecule. Therefore, an averaged picture

obtains, from the consideration of which it follows that the molecular diamagnetic susceptibility of saturated systems is an additive quantity with contributions from atoms of each species. Systems with π-bonds have an increased magnetic susceptibility since π-bonds introduce an additional contribution (increment).

The diamagnetic susceptibilities of atoms (according to Pascal), $\chi_A \times 10^6$, are as follows:

H	−2.9	F	−6.3
C	−6.0	Cl	−20.1
N	−5.55	Br	−30.6
O	−4.6	I	−44.6

The bond increments $\chi \times 10^6$ are as follows:

>C=C<	+5.5		+4.1
−C≡C−	+0.8		+3.05
−N=N−	+1.85		
>C=N−	+1.6		−0.98
−C≡N	+0.8		
>C=O	+6.32		+0.86

Adding up these values according to the formula of an organic compound, it is possible to find the value of molecular diamagnetic susceptibility calculated on the basis of additivity. The experimental value is found by measuring the weakening of the magnetic field caused by introducing the substance under study into it provided this substance does not contain unpaired electrons, i.e., have no free-radical properties, and therefore the spin magnetic moments in it are compensated in pairs and have no effect. In fact, the force required to displace the specimen from an inhomogeneous magnetic field of high strength is measured and the volume susceptibility K is found therefrom and the molecular susceptibility χ_M is calculated from the equality:

$$\chi_M = \frac{KM}{d}$$

where M = molecular weight, and d = density.

For aromatic systems, i.e., for planar cyclic systems consisting of sp^2-hybridized carbon atoms, high increments (exultations) have been detected in this way, which are proportional to the number of benzene rings.

Thus, the exultation of diamagnetic susceptibility serves as an obvious sign of aromaticity (Table 13.1).

TABLE 13.1. The Exultation of Diamagnetic Susceptibility as a Characteristic of Aromaticity

Compound	$\chi_{exp} \times 10^6$	$\chi_{cal} \times 10^6$	Difference Δ	Difference Δ / Number of benzene rings
Benzene	—55.6	—36.9	18.7	18.7
Naphthalene	—91.9	—55.7	36.2	18.1
Anthracene	—129.4	—74.5	54.9	18.3
Phenanthrene	—127.9	—74.5	53.4	17.8
Biphenyl	—102.9	—68.0	34.9	17.5
Azulene	—91	—55.7	35.3	—
Tropolone	—61	—45.8	15.2	—
Tropone	—54	—41.2	12.8	—
Cyclooctatetraene	—105.1	—79.3	25.8	—

Note: In the CGS system of units these values must be multiplied by 10^6.

It is interesting to approximately estimate the effect of ring-closure of a conjugated system of carbon-carbon bonds with an open chain on the energy of the π-electrons of the molecule. According to Heilbronner, this can be done quite simply, by applying the well-known de Broglie relation to the motion of an electron in a unidimensional potential hole having a constant potential and a completely deflecting wall. Then

$$\lambda = \frac{h}{m_e v}$$

where h = Planck's constant, and m_e and v are, respectively, the mass and velocity of the electron.

The energy quantization conditions for the electron in a linear potential box and in the ring are different. This is understandable since at each given value of energy only one kind of motion is possible in a linear potential box (the to-and-fro motion within the box), whereas in the ring two different but energetically equivalent motions are possible—the clockwise and counterclockwise movements. In other words, the energy levels are non-degenerate in the linear potential box and, generally speaking, doubly degenerate in the ring (as will be seen later, this refers to all the levels, except the lowest one). It is exactly the quantization conditions that require that the length L in the linear box be a multiple of the half-wave length $\lambda/2$ and the perimeter L in the ring be a multiple of the integral wavelength (Fig. 13.1).

Hence, these conditions have the form:

Linear potential box	Ring*
$(\lambda/2)\,n' = L \quad (n' = 1, 2, \ldots)$	$\lambda n'' = L \quad (n'' = 0, 1, 2, \ldots)$

Now for the kinetic energy we have**

$$E_{\text{kin}} = \frac{m_e v^2}{2} = \frac{(m_e v)^2}{2m_e} = \frac{h^2}{2m_e \lambda^2}$$

Imparting numerical values to the wavelength, which are allowed by the quantization conditions, we find:

Linear potential box	Ring
$E_{n'} = \frac{h^2}{8m_e L^2}\, n'^2$	$E_{n''} = \frac{h^2}{2m_e L^2}\, n''^2$
$(n' = 1, 2, \ldots)$	$(n'' = 0, 1, 2, \ldots)$

The filling of energy levels with electrons in the linear box and in the ring (in the ground state of the system) for the case of 6π-electrons (for example, for hexatriene and benzene) is shown in

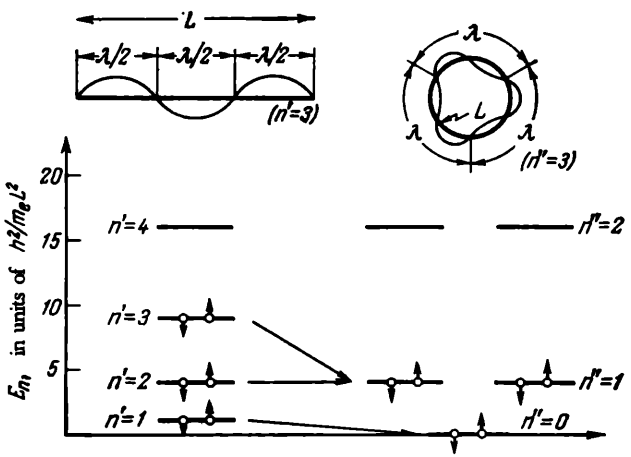


Fig. 13.1.

The model of a free electron for linear (box) and cyclic (ring) π-electron systems.

Fig. 13.1. The lower three levels ($n = 1$, $n = 2$, and $n = 3$) are occupied by three pairs of π-electrons of opposite spins, a case corresponding to six carbon atoms contained in an open conjugated system,

* $n'' = (K)$ where K proper is the true quantum number $K = 0, \pm 1, \pm 2, \ldots$, which enables the degeneracy to be written also.

** The potential energy in such models is assumed to be constant and may be taken equal to zero.

i.e., for example, 1,3,5-hexatriene. Such is its approximate model. The higher levels are the levels of the excited molecule. But if hexatriene is closed into cyclohexatriene—benzene, there will arise new quantization conditions, a consequence of the continuous electron wave. Along the perimeter L not the half-wave but the wave must lie an integral number of times, including 0, i.e., $\lambda m = L$ ($m = 0$, 1, 2, etc.)

Just as in the previous case, we obtain the values of kinetic energy for integral m (quantum values):

$$E_m = \frac{h^2 m^2}{2m_e L^2} = \frac{h^2 \cdot 2m^2}{8m_e L^2} \qquad (m = 0,\ 1,\ 2,\ \text{etc.})$$

To each value of E_m in a linear system there will correspond the only (linear) mode of motion of an electron. In the ring, however, to all the values of E_m (except E_0) there may correspond the clockwise and counterclockwise motions of the electron, which results in the probability of finding four electrons at each such level (**degenerate levels**). Only to the level E_0 there correspond, as before, two electrons. From this follows the Hückel rule—aromatic, i.e., cyclic, conjugated systems must have $4n + 2$ electrons.

The ring-closure must result in an additional stabilization of the π-electronic system. In the example presented in Fig. 13.1, this additional stabilization is equal to 12 units if the value $h^2/8m_e L^2$ is taken as a unit. From the standpoint of such additional stabilization, processes that disturb the conjugation in the ring (for example, an addition reaction) are thermodynamically unfavourable, and the transition states associated with the disturbance of conjugation show a tendency towards its recovery.

Assuming that the perimeter L of the ring is proportional to the number of electrons $(4n + 2)$ in the ring π-electron system, i.e., that $L = l\,(4n + 2)$*, we can find the value of the energy of ring-opening into a linear potential box of length L:

$$(\Delta E)_{\text{opening}} = \frac{h^2}{16m_e l^2} \cdot \frac{(n+1)}{(2n+1)}$$

As can be seen, the energy of ring-opening decreases with increasing n and, hence, with increasing ring size.

Thus, all aromatic systems may be classified according to the number of "aromatic" electrons.

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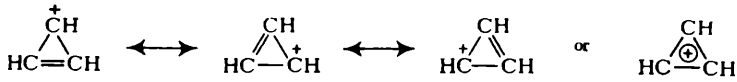
* The $(4n + 2)$π-electrons correspond to the $(2n + 1)$ formal double bonds of the structural formula.

13.2. Aromatic Systems with Two π-Electrons

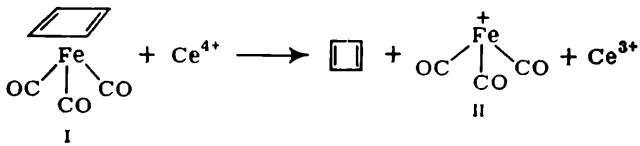
The only isocyclic aromatic system of this series must be the hypothetical **cyclopropenylium ion**:



A number of derivatives of the cyclopropenylium cation are known. The first representative, triphenylcyclopropenylium cation, was obtained by Breslow in 1961. This compound is highly stable: neither the action of bromine nor that of hydrogen over a catalyst makes this cation show ordinary reactions of disruption of the three-membered ring and addition across the double bond.

13.3. Aromatic Systems with Four π-Electrons

According to Hückel, cyclobutadiene which has two π-bonds and, hence, four π-electrons, can have no aromatic character. Indeed, cyclobutadiene at the moment of separation from a complex by the reaction (Pettit, 1966):



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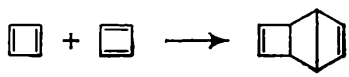
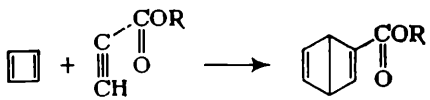
possesses the properties of an energetic diene and of a dienophile at the same time. Having been isolated, it immediately dimerizes



and in the reaction with acetylenecarboxylic ester it behaves as a diene, forming the derivatives of Dewar benzene:

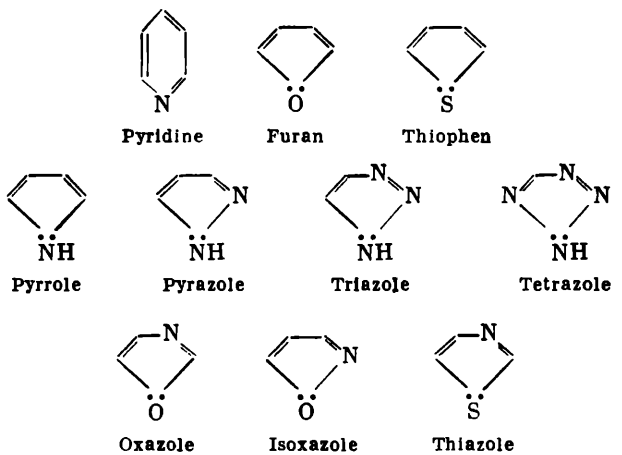


But, in the form of a complex I with iron tricarbonyl, cyclobutadiene behaves as a true aromatic compound (it is no longer a monocyclic system).

Pettit and his coworkers, who carried out the investigations just mentioned, effected the acylation of complex I through the Friedel-Crafts reaction, deuteration with deuteroacetic acid, the Mannich dimethylaminomethylation, chloromethylation by formaldehyde with hydrochloric acid, formylation with methylformanilide and $POCl_3$, and mercuration.

13.4. Aromatic Systems with Six π-Electrons

Apart from benzene and other benzenoid systems, the following aromatic heterocycles contain six π-electrons:



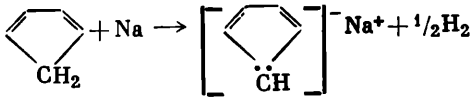
and others. They have already been discussed (see Volume III).

Among the isocyclic non-benzenoid aromatic systems with six π-electrons the most important and structurally simple are the cyclopentadienyl anion and the tropylium cation.

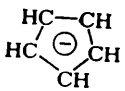
A. The Cyclopentadienyl Anion

Cyclopentadiene (Volume II, page 234), which is contained in the pyrolysis products of petroleum fractions and in the benzene fraction of coal tar, is a typical unsaturated hydrocarbon with two conjugated π-bonds. When cyclopentadiene is reacted with sodium (in a solution of ethyl ether or tetrahydrofuran), the following reac-

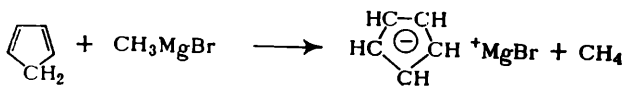
tion takes place:



Sodium gives its electron to the proton being detached from the cyclopentadiene molecule, converting it into atomic hydrogen, which is partially consumed for the reduction of the second cyclopentadiene molecule to cyclopentene. The sodium cation becomes electrostatically bound to the cyclopentadienyl anion, in which the four electrons of the π-bonds and the electron pair of the carbon atom left after the detachment of a proton form a "delocalized" aromatic sextet. The five-membered ring is now formed by five equivalent CH groups and the cyclopentadienyl anion may be represented as follows:



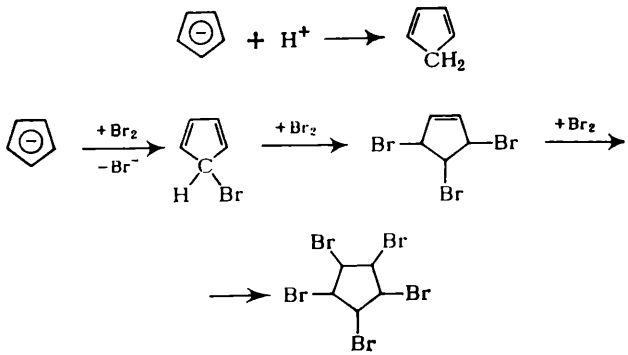
The same result can be achieved by the action of strong bases (such as sodamide) or a Grignard reagent on cyclopentadiene:



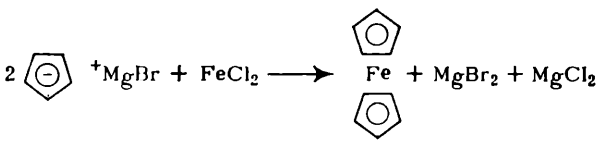
Such a system is energetically poorer than could be expected from the cyclopentadienyl anion with normal double bonds and the charge localized on one of the five carbon atoms. The hydrogen ion in cyclopentadiene leaves the molecule so readily in the above reactions exactly because the stable, low-energy anion is left and the process is energetically favourable. The hydrogen atom leaves the molecule just as readily in the form of a proton in a number of condensation reactions (with aldehydes and ketones, see Volume I, page 187). In the presence of bases cyclopentadiene exchanges, for the same reasons, all its six hydrogen atoms for deuterium under the action of D_2O (D. N. Kursanov, Z. N. Parnes).

Although the cyclopentadienyl anion is undoubtedly aromatic and is a non-alternant aromatic system, it is impossible to demonstrate this directly by ordinary means because of the difficulty of addition reactions and the tendency towards electrophilic substitution reactions since we are speaking here of a charged molecule—an anion. Any electrophilic reagent attacks the molecule having an extra electron (the negative charge of the anion) and adds to one (it is

immaterial which) of the five carbon atoms, destroying the aromaticity of the system and converting the cyclopentadienyl anion into a substituted cyclopentadiene:



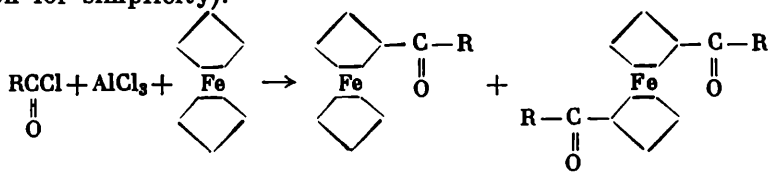
If, however, as has been established by Pauson, cyclopentadienylmagnesium bromide is acted on by ferrous chloride (ferric chloride may also be used because it is reduced to the ferrous state), then a very interesting aromatic system is formed—**iron dicyclopentadienyl** or **ferrocene**, which has been shown by X-ray analysis to have a sandwich structure (Woodward, Wilkinson):



In ferrocene, the cyclopentadienyl rings attached to the central metal atom (page 103) bear each a partial negative charge of the anion and not the full charge. According to quantum-mechanical calculations by means of the molecular orbital method (M. E. Dyatkina and E. M. Shustorovich), it is —0.35 of the electronic charge on each of the rings (+0.7 on iron). It is for this reason that the cyclopentadienyl rings are much less susceptible to nucleophilic attack than the cyclopentadienyl anion and are incapable of adding electrophilic reagents, except under vigorous conditions with the destruction of the entire system (for example, under the action of bromine, in which case the cyclopentadienyl rings are eliminated in the form of pentabromocyclopentane). Ferrocene does not exchange, like cyclopentadiene, its hydrogen atoms for deuterium in the presence of bases: it enters into a deutero-exchange reaction only with strong deutero acids of the type D_2SO_4, like benzene, but at a higher velocity (D. N. Kursanov, V. N. Setkina).

The first electrophilic substitution reaction of ferrocene was the Friedel-Crafts acylation discovered by Woodward and Rosenblum,

which leads to the formation of mono- and diketones of ferrocene (hereafter the ferrocene ring will be represented as an ordinary pentagon for simplicity):

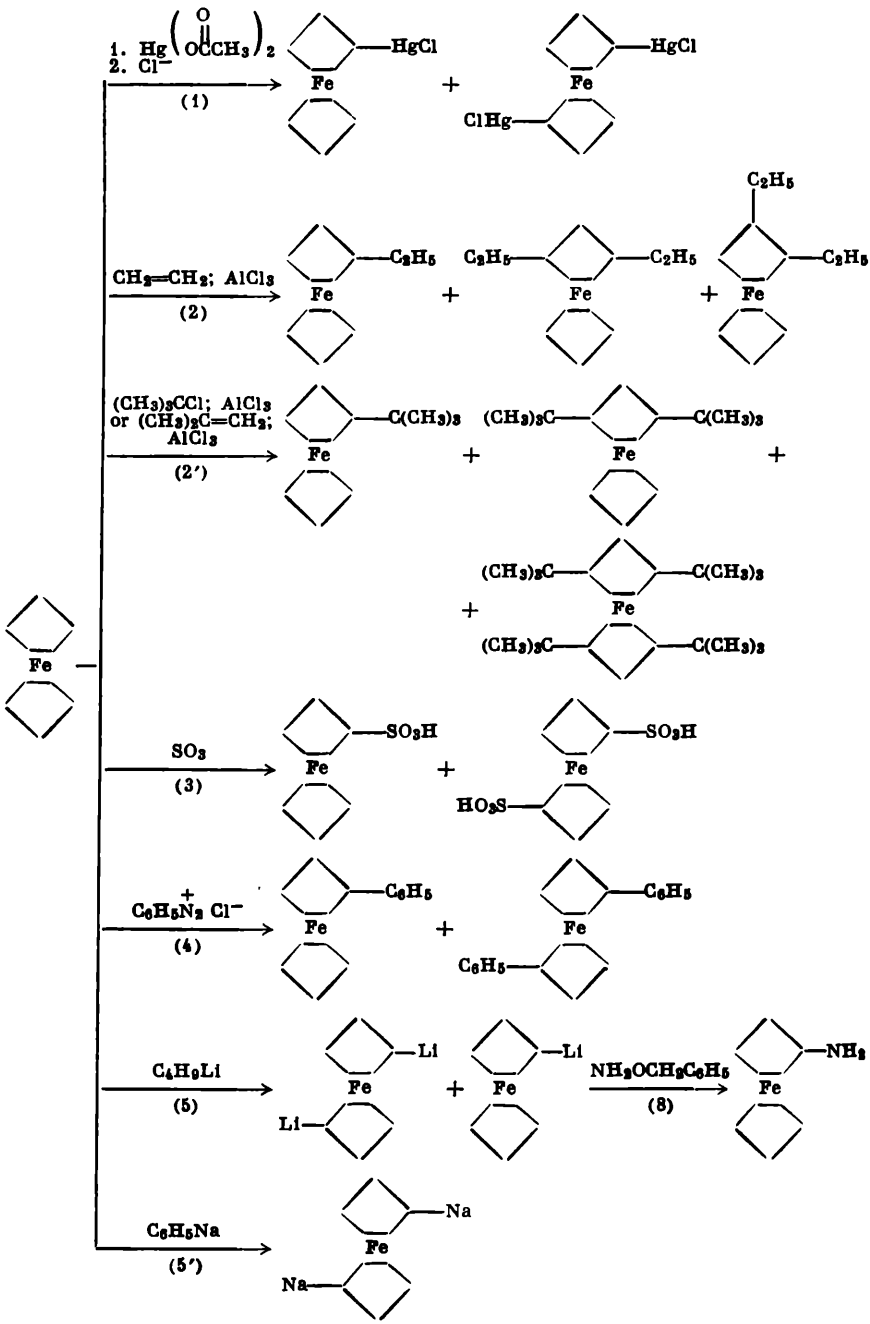


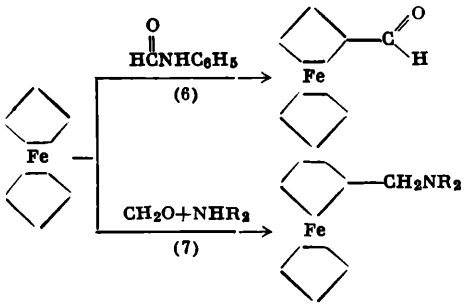
However, under these conditions cycloalkanes too undergo acylation, and at first the aromaticity of ferrocene was doubtful, the more so that the ordinary reagents used for electrophilic substitution in benzene (nitric acid, the halogens, and even sulphuric acid) detach one electron from ferrocene, converting it into the **ferricenium ion**, which is incapable of undergoing electrophilic attack.

Dunitz and Orgel have established, by means of detailed X-ray analysis, that the carbon-carbon bond distance in ferrocene is equal to 1.41 Å, which corresponds to that of an aromatic systems. The Fe—C distance, 2.03 Å, is equal to the sum of the covalent radii of iron and carbon (linked by a single bond). The distance between the planes of the cyclopentadienyl rings is 3.41 Å.

The rotation of the cyclopentadienyl rings about the axis passing through the iron atom and the centres of the cyclopentadienyl rings is unhindered. A number of ferrocene derivatives have been studied by Yu. T. Struchkov by means of X-ray analysis.

The pioneering studies that have provided a conclusive chemical evidence for the aromatic character of ferrocene are due to A. N. Nesmeyanov and his coworkers, E. G. Perevalova, R. V. Golovnya, O. A. Nesmeyanova, N. S. Kochetkova, and S. S. Churanov. They have succeeded in carrying out the following reactions on ferrocene (see page 146): (1) mercuration; (2) alkylation by the Friedel-Crafts reaction; (3) sulphonation under the conditions of the Terentiev reaction with sulphur trioxide (at about the same time Weinmayr effected the sulphonation of ferrocene by means of sulphuric acid in acetic anhydride); (4) arylation (simultaneously with Pauson) by the Gomberg reaction with aryldiazonium salts (a free-radical reaction, see Volume III, page 126); (5) metalation by butyllithium and phenylsodium (5′), just as in the case of "superaromatic compounds" (A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya, and O. A. Nesmeyanova; Benkeser). Pauson, using the Vilsmeier reaction, succeeded in obtaining **ferrocene aldehyde** by the action of formanilide on ferrocene (6) in the presence of H_2SO_4; this compound behaves as an aromatic aldehyde. Ferrocene also undergoes the Mannich reaction (7)—formaldehyde with dialkylamines, as a result of electrophilic attack, dialkylaminomethylates ferrocene (see the scheme on pages 146-147).

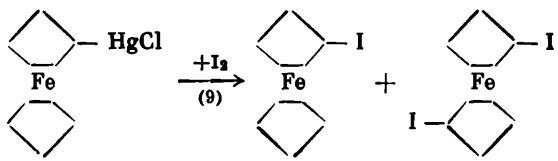

1. Hg(OCCH3)2
2. Cl−
(1)
HgCl
ClHg
Fe
CH2=CH2; AlCl3
(2)
C2H5
(CH3)3CCl; AlCl3
or (CH3)2C=CH2; AlCl3
(2′)
C(CH3)3
SO3
(3)
SO3H
HO3S
+
C6H5N2 Cl−
(4)
C6H5
C4H9Li
(5)
Li
C6H5Na
(5′)
Na
NH2OCH2C6H5
(8)
NH2



Aminoferrocene (ferrocenylamine) has been prepared by means of the reaction (8) developed by K. A. Kocheshkov (A. N. Nesmeyanov and E. G. Perevalova). It has proved a stronger base than aniline and incapable of undergoing diazotization; in other respects, it behaves like aromatic amines: forms Schiff's bases with aromatic aldehydes.

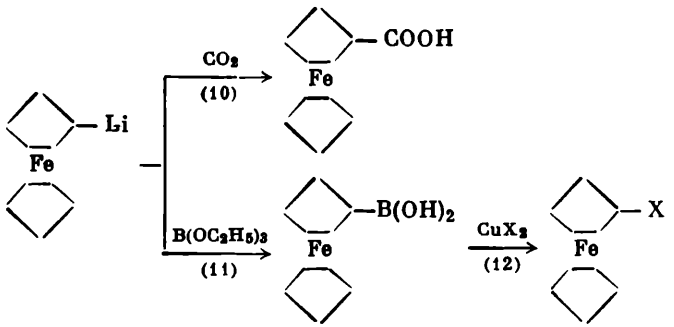
The reactions given include electrophilic substitutions which are typical of aromatic (more precisely, superaromatic) rings. Metalation, free-radical substitutions, the behaviour of an amine and an aldehyde, all these provide a full analogy not so much with benzene itself as with superaromatic compounds such as thiophen, furan, and phenol.

The first halogen derivatives of ferrocene prepared from its mercury derivatives by the action of iodine (9) were iodoferrocene and diiodoferrocene, in which the iodine enters into exchange reactions with nucleophilic reagents only in the presence of a copper catalyst (O. A. Nesmeyanova):

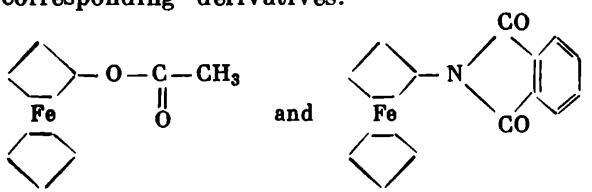


Organometallic compounds of ferrocene have been used in numerous syntheses (A. N. Nesmeyanov, V. A. Sazonova, V. N. Drozd). For example, the action of CO_2 on a lithio derivative gives **ferrocenecarboxylic acid** (10) and **ferrocenedicarboxylic acid**, and the action of $B(OC_2H_5)_3$ yields **ferrocenylboronic acid** (11) and **ferrocenyldiboronic acid.** From ferrocenylboronic acids by the reaction with a cupric halide (12) there have been obtained **chloroferrocene** and **bromoferro-**

cene

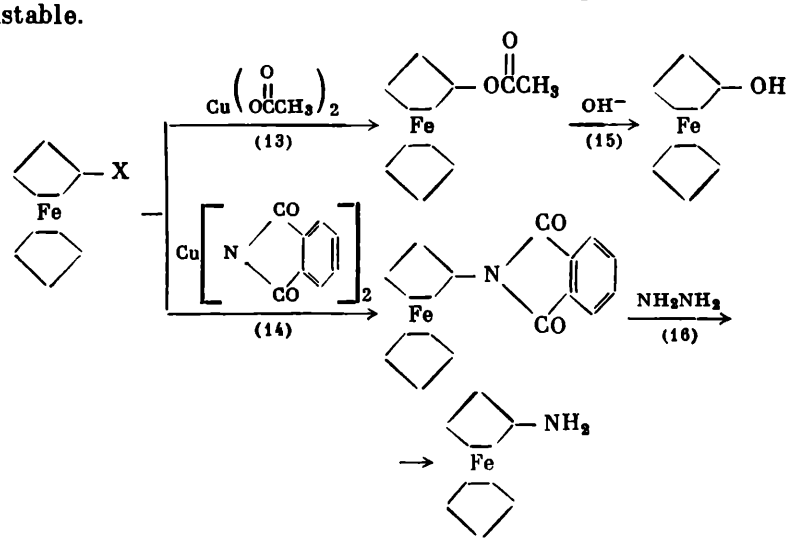


and, respectively, the dihalides. The halogen in these derivatives behaves as a typically aromatic halogen and is but only slightly liable to exchange reactions. It is exchanged, however, with copper salts of carboxylic acids (13) and with copper phthalimide (14) to form the corresponding derivatives:



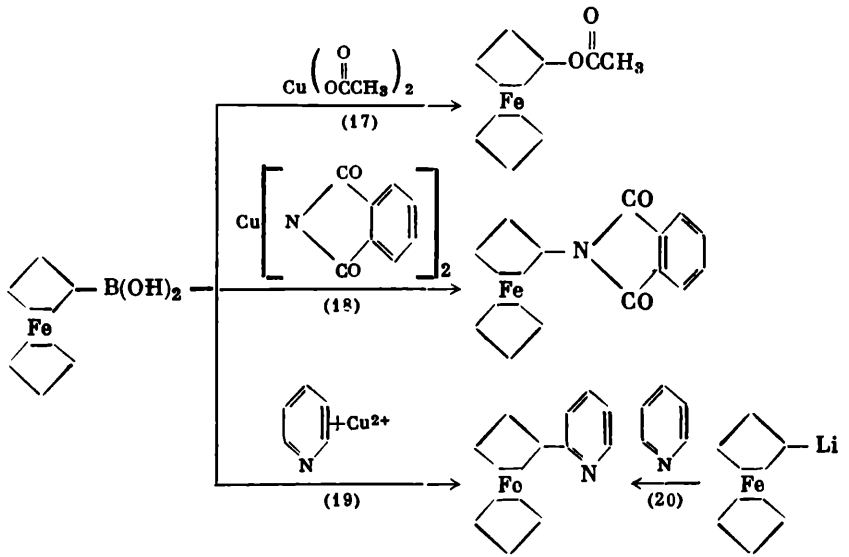
The hydrolysis of the first of them (15) gives **ferrocenol**, and the hydrazinolysis of the second (16) affords **ferrocenylamine** [see also reaction (18)].

Ferrocenol is an acid three times weaker than phenol and is highly unstable.

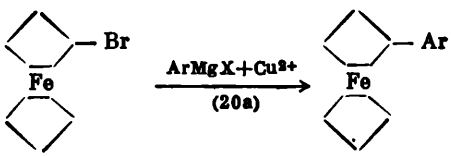


An analogous route leads to the synthesis of 1,1′-dihydroxyferrocene and 1,1′-ferrocenylenediamine, and also [by exchange with $Cu_2(CN)_2$] of mono- and dinitriles of ferrocenecarboxylic acids.

It has been found that the direct action of cupric salts of carboxylic acids on ferrocenylboronic acid (17) and also of copper N-derivatives, such as cupric phthalimide (18), leads to the replacement of the boronic acid function by the anion. Even with pyridine in the presence of cupric carbonate (19) there is formed α-ferrocenylpyridine, which is prepared in better yields by the action of ferrocenyllithium on pyridine (20).

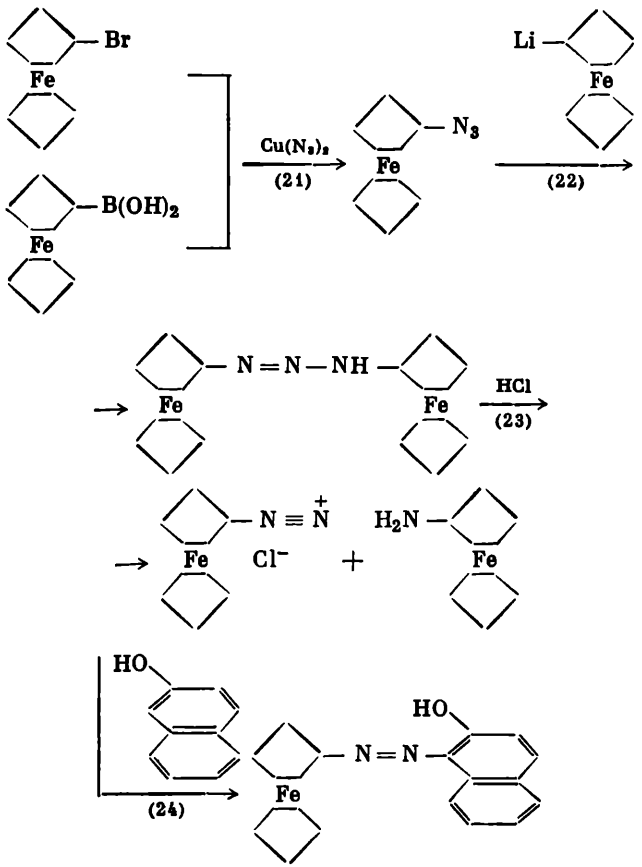


Another route to ferrocenyl heterocycles is by the action of a Grignard reagent, a derivative of the corresponding heterocycle, on bromoferrocene in the presence of a copper salt. When arylmagnesium bromide is reacted with bromoferrocene under these conditions, (20a), an arylferrocene is obtained, which is the second independent route for synthesis of arylferrocenes:



The action of copper on iodoferrocene unites ferrocene radicals into **diferrocenyl**, and from 1,1′-diiodoferrocene and iodoferrocene there is obtained terferrocenyl in this way.

When bromoferrocene (or ferrocenylboronic acid) is allowed to react with copper azide (21), ferrocenylazide results, from which, by the action of ferrocenyllithium, diazoaminoferrocene is obtained, which is converted by acidolysis (23) into a mixture of ferrocenylamine and ferrocenyldiazonium, the latter being capable of azo coupling and forming, say, with β-naphthol, 1-ferrocenyl-2-azonaphthol (24).



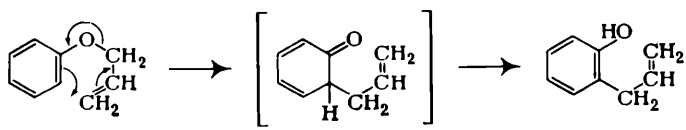
An extraordinary reaction in the ferrocene series is the **direct cyanation** of the corresponding cation with hydrocyanic acid, leading to the nitrile of a ferrocenecarboxylic acid and its 1,1'-dinitrile. Ferrocene derivatives also undergo cyanation, in which case electron-accepting substituents (see page 152) direct the cyano group into the other ring, while electron-donating groups orient it into the same ring (A. N. Nesmeyanov, E. G. Perevalova). The homologues of

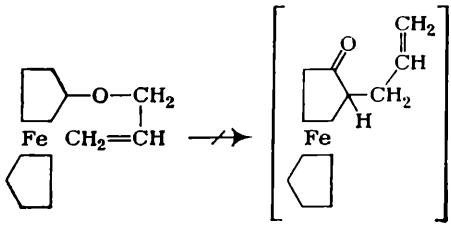
ferrocene have been prepared by direct alkylation by the Friedel-Crafts reaction (N. S. Kochetkova) by reducing, with lithium aluminium hydride, the esters of ferrocenecarboxylic acid (the methyl homologue, E. G. Perevalova) and by reducing acylferrocenes (N. A. Volkenau).

The investigation of electrophilic substitution reactions in the homologues and other derivatives of ferrocene has enabled us to arrive at the conclusion that ferrocene is an aromatic entity (and not two isolated aromatic cyclopentadienyl rings) and that the influence of substituents is transmitted from one ring to the other in nearly the same manner as in the benzene ring from the *meta*-position. The substituent, however, exerts a greater effect on the ring in which it is situated, as was established for the first time by N. A. Nesmeyanov and O. A. Reutov on a series of ferrocenecarboxylic acids (synthesized by them) having the following substituents in the other cyclopentadienyl ring:

$$SO_2NH_2, \quad SO_2F, \quad CN, \quad R-\overset{\overset{O}{\|}}{C}-, \quad RO-\overset{\overset{O}{\|}}{C}-, \quad Alk$$

From the examples of Friedel-Crafts alkylation and acylation reactions of ferrocene it can be seen that an electron-accepting group (for example, the acetyl group) deactivates the cyclopentadienyl ring it has entered more strongly than the other ring, and the next acetyl group enters the latter ring. The ethyl group activates the cyclopentadienyl ring it has entered more strongly than the other ring, and the second ethyl group replaces the hydrogen in the same ring, which leads to a mixture of two isomeric homoannular diethylferrocenes—1,2-diethylferrocene and 1,3-diethylferrocene, the 1,3-isomer predominating. Such a substitution is a typical reaction. Here are manifested the properties of a non-alternant aromatic system. The orientation is determined by the total enhanced nucleophilic character of the ring due to the $+I$ effect of the ethyl group, without alternation of this nucleophilicity at odd and even atoms. The predominance of the 1,3-isomer over its 1,2-counterpart is accounted for by the greater steric hindrances to the formation of the latter. The non-alternant character is evidently also responsible for the impossibility in the ferrocene ring of rearrangements so typical of the benzene ring: the Claisen rearrangement of the allyl ether of phenol to *o*-allylphenol (A. N. Nesmeyanov, V. A. Sazonova):





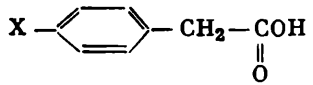
Because of the non-alternant character of the cyclopentadienyl system the formation of a reaction complex with a quinonoid arrangement of double bonds, just as in benzene, is impossible, and the rearrangement fails to occur.

Other ring rearrangements characteristic of the benzene ring do not occur either. Thus, the azoferrocenes prepared by A. N. Nesmeyanov, E. G. Perevalova, and T. V. Nikitina, when reduced to hydrazoferrocenes, do not rearrange to the corresponding benzidines.

Extremely interesting are the results obtained by S. P. Gubin and E. G. Perevalova who carried out a quantitative study of the effect of substituents X in the ferrocene ring on the redox potential of the reversible reaction

$$XC_5H_4FeC_5H_5 \underset{+e}{\overset{-e}{\rightleftarrows}} XC_5H_4Fe^+C_5H_5$$

and also on the dissociation constants of substituted carboxylic acids of ferrocene $XC_5H_4FeC_5H_4COOH$. In the first reaction, the substituents decrease the oxidation potential if they are electron-donating substituents, and direct the electrophilic substitution into the same cyclopentadienyl ring in which they are situated (X in this case are the *ortho-para* directors). But with electron-accepting substituents the redox potential increases. The logarithms of these potentials (ordinates) lie on a straight line if the Taft constants σ^0_{para} for a number of substituents X are plotted along the abscissa (the Hammett equation $\log K = \sigma^0\rho$, see Volume III, page 224). These constants were derived by Taft on the basis of measurements of the dissociation constants of a number of acids of the type



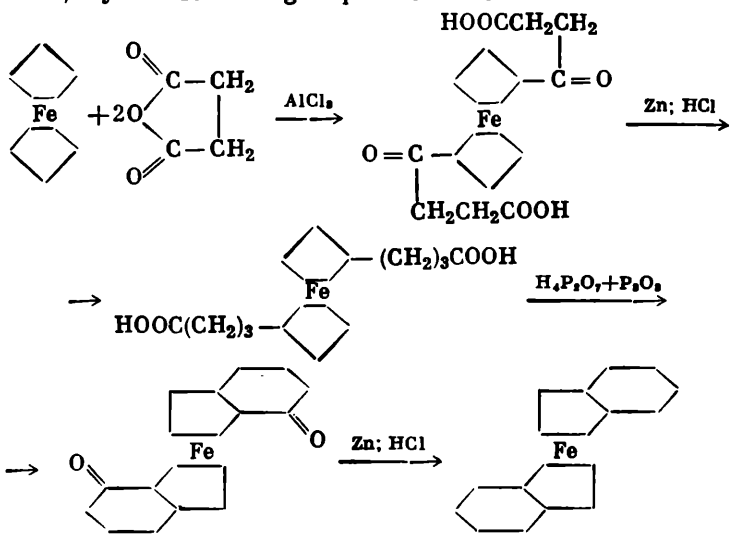
that is, acids in which the effect of substituent X transmitted through the benzene ring reaches the carboxyl group only by the inductive effect via the CH_2 group which disrupts the conjugation. The dissociation constants of $XC_5H_4FeC_5H_4COOH$ are characterized by the same values of σ^0_{para} for substituents X. All this means that the effect of the substituent in one cyclopentadienyl ring is transmitted

to the central iron atom being oxidized or to the other ring by the inductive effect (the *I* effect) and not by the *T* effect, as is the case in the benzene ring from the *para*-position.

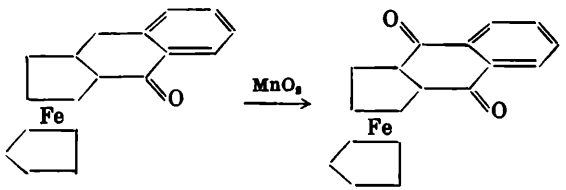
It is however interesting to note that substituents X are classified with respect to ferrocene into electron-donating and electron-accepting in a different manner than with respect to the benzene ring. Thus, only the alkyl groups are electron-donating with respect to ferrocene (the amino group has not been measured); the halogens, —OH, —OCH_3, —NH—C(=O)—CH_3 and even —HgCl, not to mention —C(=O)—OH and —C(=O)—R, are electron-accepting. This is also revealed in the interactions between the benzene ring and ferrocene in phenylferrocene. The nitration of phenylferrocene gives *p*-nitrophenylferrocene, i.e., the ferrocenyl substituent acts as an electron-donating *ortho-para* director. On the contrary, in the dimethylaminomethylation reaction by means of tetramethyldiaminomethane (a modification of the Mannich reaction) gave 1-phenyl-1′-dimethylaminomethylferrocene, i.e., the phenyl group as a *meta* director oriented the electrophilic substitution reaction into the other cyclopentadienyl ring.

E. Fischer synthesized diindenyliron (benzoferrocene), using an indenylmagnesium halide as the starting material. He hydrogenated diindenyliron to di-(tetrahydroindenyl)-iron.

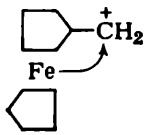
A. N. Nesmeyanov, N. A. Volkenau, and V. D. Vil'chevskaya prepared the last-named compound, which is identical with the Fischer compound, by the following sequence of reactions:



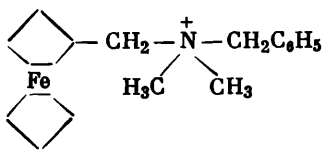
In an analogous way, by the action of phthalic anhydride there has been obtained a derivative which is readily oxidized to the analogue of anthraquinone—dark-violet crystals (A. N. Nesmeyanov, N. S. Kochetkova and V. D. Vil'chevskaya):



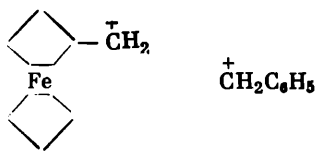
The properties of the carbon atom in the α-position with respect to the cyclopentadienyl ring are interesting. The sharp stabilization of the α-carbonium ion was first noted by Richards, who ascribed it to the direct mesomeric transfer of electrons by the iron atom to the carbonium ion.



E. G. Perevalova and Yu. A. Ustynyuk carried out ferrocenylmethylation by quaternary ammonium salts of the type



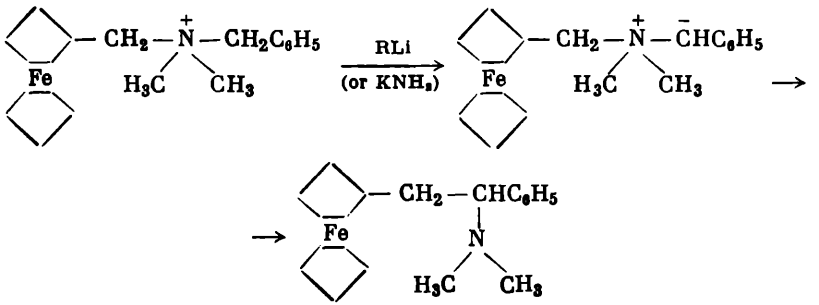
in a reaction, say, with the hydroxyl ion, which made it possible to compare the abilities of the carbonium ions—the ferrocenylmethyl cation I and the benzyl cation II—to be detached:



I II

It has turned out that the hydroxyl group is alkylated invariably by the ferrocenylmethyl ion and not by the benzyl ion; the reaction proceeds as a substitution reaction of the S_N1 type. This means that the ferrocenylmethyl cation is considerably more stable than the benzyl cation.

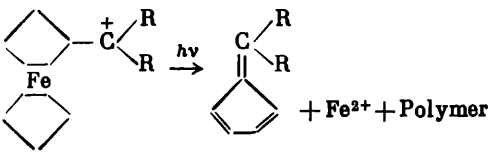
As has been shown by the studies accomplished by the same authors, the situation is quite different with the stabilization of the carbanion and the radical by the ferrocenyl. Thus, the Stevens rearrangement, which occurs with ammonium salts of the same type under the action of a strong base which splits off a proton from one of the CH_2 groups linked to the ammonium nitrogen, invariably proceeds in the direction showing that the phenyl group stabilizes the neighbouring anionic centre to a greater extent than does the ferrocenyl:



Upon reduction with sodium amalgam in water the benzyl radical is eliminated in the form of toluene, leaving the ferrocenylmethyl radical linked to nitrogen.

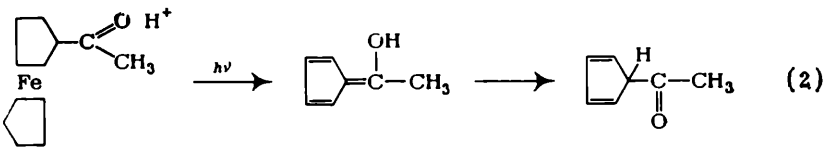
There has recently been obtained the **triferrocenylmethyl cation** which is very stable.

According to the studies carried out by A. N. Nesmeyanov and V. A. Sazonova ferrocenylmethyl cations are unstable towards light and decompose with the formation of fulvenes; for example,



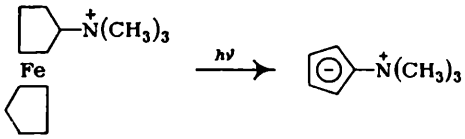
(1)

It appears that all ferrocene compounds that bear a full or partial positive charge on the α-atom are susceptible to photolysis which results in the formation of fulvenes or ylides* (**cyclopentadienylides**). For instance:

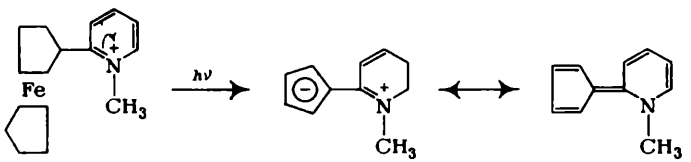


(2)

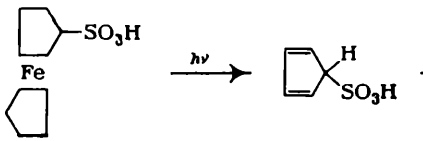
* This term was introduced by Wittig who was the first to investigate these compounds.



(3)



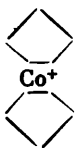
(4)



(5)

Reactions of the type (3) are a new route for synthesis of certain ylides of nitrogen (see below).

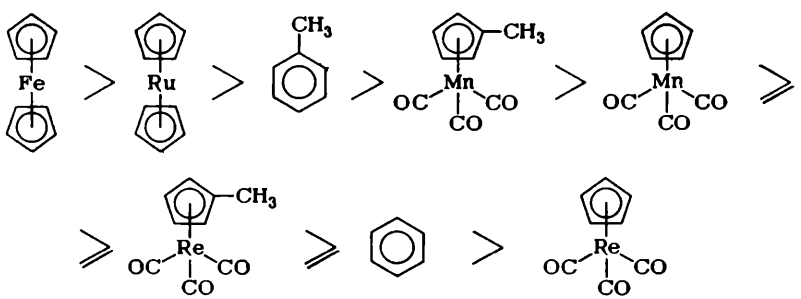
Ferrocene is not the only aromatic sandwich system. Exceedingly stable is the **cobalticenium ion** which is isoelectronic with ferrocene:



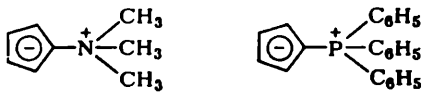
Because of its positive charge this cation, however, is incapable of undergoing electrophilic substitution reactions.

The cyclopentadienyl derivatives of ruthenium and osmium, **ruthenocene** and **osmocene**, are similar to ferrocene, being less superaromatic though, i.e., they undergo electrophilic substitutions somewhat less readily than ferrocene.

Based on the rate of deuteration in acid medium, D. N. Kursanov and V. N. Setkina have established the following aromaticity series of sandwich organometallic compounds:

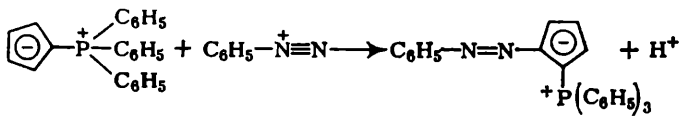


Other aromatic systems in which the cyclopentadienyl ring assumes a negative charge are the so-called **ylides.** As examples may serve the following structures:

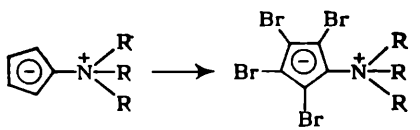


In these compounds, the negative charge of the five-membered ring is compensated intramolecularly by the positive charge of the ammonium or phosphonium moiety of the molecule. Ylides have a high dipole moment; for example, the dipole moment of triphenylphosphoniumcyclopentadienylylide given above is 7 D.

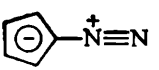
Aromatic reactions of ylides may be exemplified by the azo coupling with the phenyldiazonium cation:



or by the bromination effected by Sazonova:

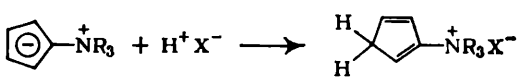


Still another example of ylides is **diazocyclopentadiene** having the structure



Finally, the negatively charged cyclopentadienyl ring is present in the bicyclic system of azulene (page 163).

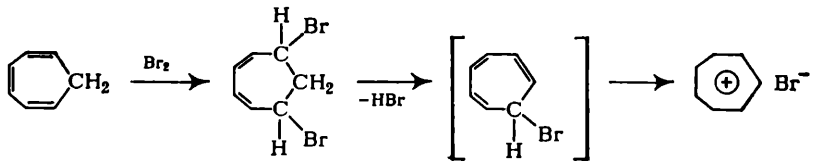
All ylides readily capture a proton from acids, being thus converted into substituted cyclopentadienes:



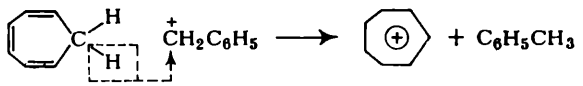
As a result of this, their properties are sharply altered, they lose aromatic character and change light absorption, functioning as indicators.

B. The Tropylium Ion

In a certain sense, the antipode of the cyclopentadienyl anion is the **tropylium ion.** If a bromine molecule is added (1,6-addition) to cycloheptatriene (tropilidene) followed by the removal of one molecule of HBr, the remaining bromine atom leaves the molecule on its own at the same time as an anion, as a result of which the tropylium ion (cycloheptatrienyl cation) is left (Doering):

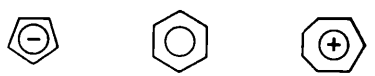


The tendency to form the stable aromatic system of the tropylium ion is so great that, as has been found independently by D. N. Kursanov and M. E. Volpin and H. J. Dauben, cycloheptatriene readily loses a hydride ion under the action of an appropriate acceptor, say, the triphenylmethyl or the benzyl cation:



While the six aromatic electrons in the cyclopentadienyl anion are distributed among the five carbon atoms, the aromatic sextet in the tropylium ion is spread over the seven carbon atoms of the ion.

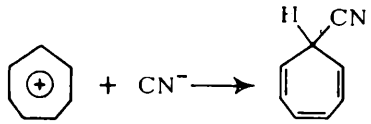
Let us compare once more the three isocyclic aromatic systems:



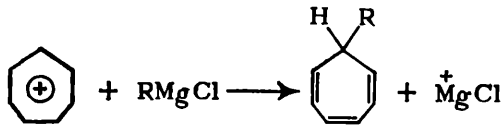
All the three systems are planar. This is the necessary condition of aromaticity.

The cyclopentadienyl anion even in the form of sandwich metallic derivatives with a weakened negative charge are extremely susceptible to electrophilic attack. Benzene is a neutral molecule. The tropylium ion is completely inert to electrophilic attack and does not undergo substitution reactions typical of benzene (and ferrocene), but is highly susceptible to nucleophilic attack. However, this involves not a substitution but an addition reaction in which the aromaticity is destroyed and the cycloheptatriene system is

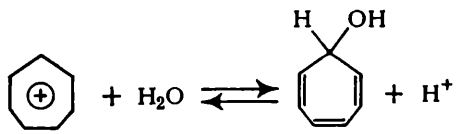
formed:



A similar reaction takes place in the presence of reactive organometallic compounds (reactions with carbanions). Thus, under the action of a Grignard reagent the tropylium ion is converted into an alkylcycloheptatriene (or an arylcycloheptatriene):

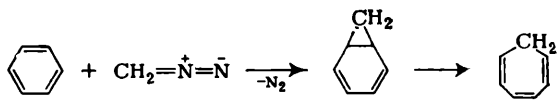


In aqueous solutions of tropylium salts the following equilibrium is set up:



Thus, the tropylium ion gives an acid reaction in aqueous solution; it is a Lewis acid and is equal in strength to acetic acid. Therefore, tropylium salts exist only with anions of strong acids. The anions of weak acids, i.e., anions liable to form covalent bonds (and, therefore, also the corresponding weak acids) react in the same manner as the cyano anion.

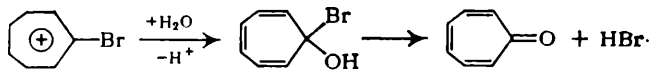
Of interest are the reactions of conversion of the tropylium cation into benzene derivatives. Thus, when a tropylium salt is oxidized with chromic anhydride or potassium permanganate, benzaldehyde is formed. The reverse route is also possible: from benzene via norcaradiene to the tropylium cation by means of the following reactions:



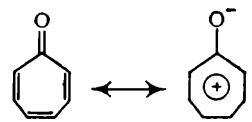
this being followed by the reactions indicated above.

A special place among the derivatives of the tropylium ion is occupied by **tropone** (*cycloheptatrienone*), a ketone which can be

prepared by the hydrolysis of the bromotropylium cation:

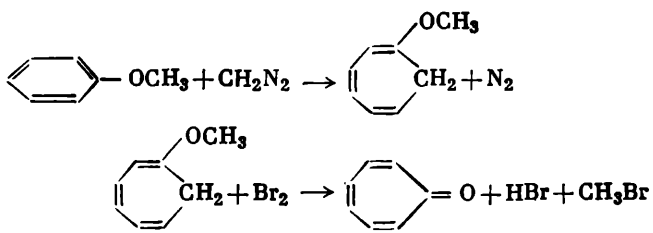


Many of the properties of this ketone, both physical (high dipole moment, 4.17 D) and chemical (inertness to the action of bromine), point to the structure of tropone being shifted to the betaine structure:

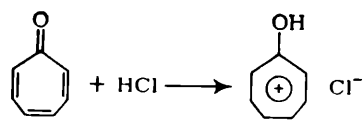


If tropone had the complete betaine structure, its dipole moment would have been considerably higher.

Tropone can also be prepared by the expansion of the benzene ring under the action of diazomethane on anisole. The first step of the reaction is the conversion of anisole into methoxyheptatriene which is converted into tropone by the action of bromine:

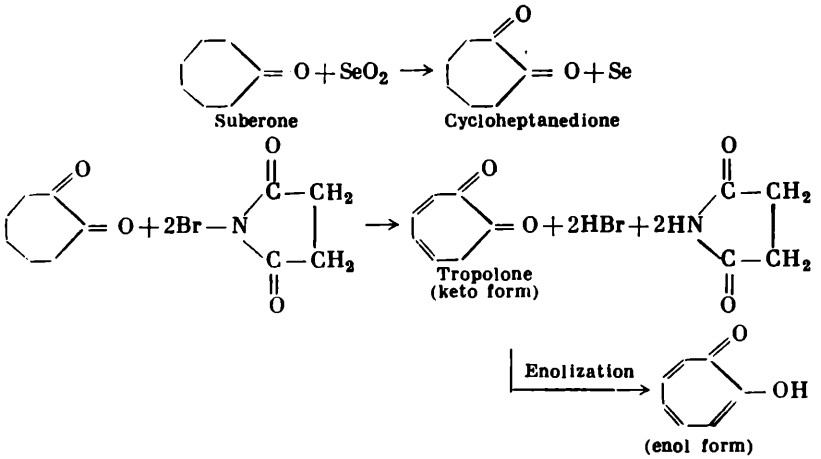


Tropone is a weak base which forms a salt with hydrogen chloride:



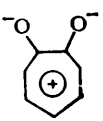
The most interesting compound having the tropone structure as the basic unit is **tropolone.** This compound can be obtained by the dehydrogenation of cycloheptanedione under the action of bromosuccinimide. Cycloheptanedione in its turn is obtained from suberone by the oxidation of the α-methylene unit into a carbonyl by means

of selenium dioxide:



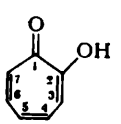
The action of bromine on 2-hydroxycycloheptanone (dehydrogenation with bromine) also leads to the stable structure of tropolone.

Tropolone is aromatic. It has a lower energy than required by the additive scheme (by 29 kcal/mole less). The dipole moment of tropolone is 3.59 D. Tropolone is a weak acid and is intermediate in strength between acetic acid and phenol ($pK_a = 6.92$). Upon its dissociation a symmetrically built anion is formed:

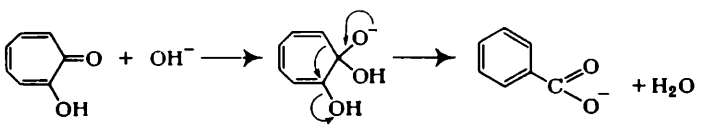


Tropolone is similar to phenols in many respects. Like phenols, it gives a coloured compound under the action of ferric chloride, and forms esters with anhydrides and acid chlorides (but not with acids). The ethers of tropolone prepared by alkylation with dialkyl sulphates or diazoalkanes are hydrolysed much more readily than phenol ethers, and therefore more closely resemble esters of acids. At the same time tropolone is a base capable of trapping hydrogen ion and forming complexes, say, with the copper ion.

In contrast to tropones, tropolones readily enter into electrophilic substitution reactions. These reactions occur in positions 3, 5, and 7.

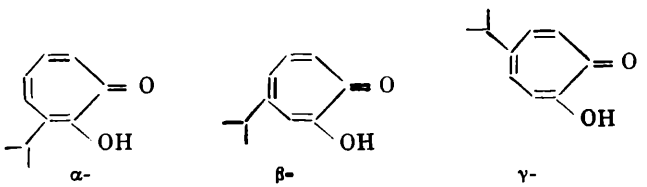


The tropolones can be halogenated, nitrated, nitrosated; with aryldiazonium cations they form arylazotropolones; they enter into the Mannich reaction (aminomethylation). By making use of the Reimer-Tiemann reaction it is possible to introduce an aldehyde group into tropolone by the action of chloroform in alkaline medium. Tropolone cannot, however, be alkylated and acylated by the Friedel-Crafts reaction. When allowed to react with nucleophilic reagents, say, alkali, the tropolones (especially substituted tropolones which have electron-attracting substituents) rearrange to derivatives of benzoic acid:

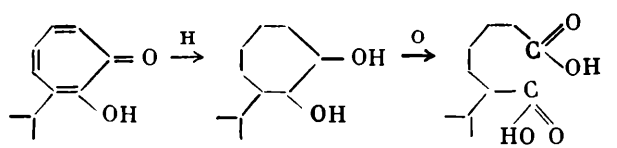


This reaction makes it possible to elucidate relatively easily the position of substituents in the ring and is widely employed for structure determinations.

Like many stable aromatic systems, tropolone in the form of its derivatives is rather widely distributed in nature in the plant kingdom, which became known only in the period 1940-1950. Of the natural compounds having the tropolone structure mention should be made of terpenic tropolones, α-, β-, and γ-**thujaplicins**, which occur in the cedar wood:

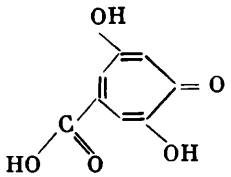


Their structure has been established by reduction to the corresponding isopropylcycloheptanediol and oxidation of the latter to isopropylpimelic acid with the same position of the isopropyl group:

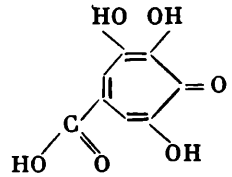


α-Thujaplicin — Isopropylpimelic acid

The following tropolone derivatives have been found in moulds of the various species:

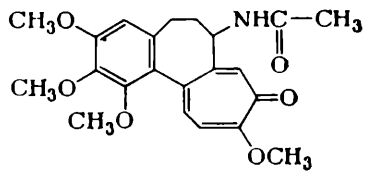


Stipitatic acid



Puberulic acid

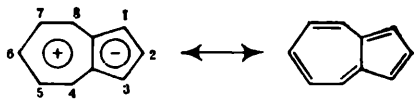
Some bulbous plants of the *Lilaceae* family and the *Colchicum* species (crocus) contain the alkaloid **colchicine** which has become especially known owing to its remarkable property of affecting heredity by doubling chromosomes in plants. In 1945 Dewar forecast that the tropolone ring would be found to be contained in the structure of colchicine and at a later time its structure was established:



13.5. Aromatic Systems with More Than Six π-Electrons

A. Azulene

The following condensed bicyclic compound which consists of the tropylium ring fused to the cyclopentadienyl ring and which is known as bicyclo[5.3.0]decapentaene

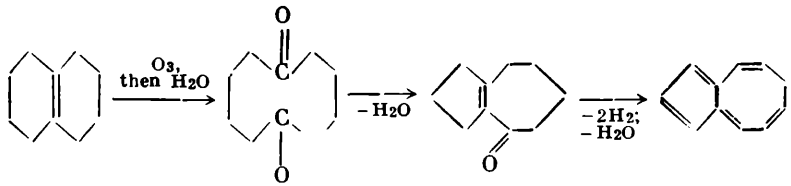


(*a*) (*b*)

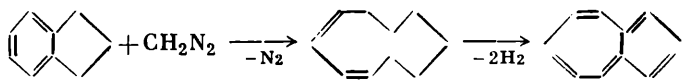
was named **azulene** because of its intense blue colour. The dipole moment of azulene is only 1.0 D. Though this is a high dipole moment for a hydrocarbon, it is much lower than required by formula *a*. It should therefore be assumed that the completely non-polar structure *b* is of greater importance in the description of the azulene

structure. The resonance energy of azulene is however lower (by 45 kcal/mole) than that of the corresponding hypothetical hydrocarbon of structure *b* with isolated localized double bonds.

One of the first routes for synthesis of the azulene bicyclic system was the intramolecular croton condensation of the diketone 1,6-cyclodecanedione, leading to the bicyclic ketone $\Delta^{9(10)}$-bicyclo[5.3.0]dece-4-none. Its dehydrogenation accompanied by dehydration yields azulene:

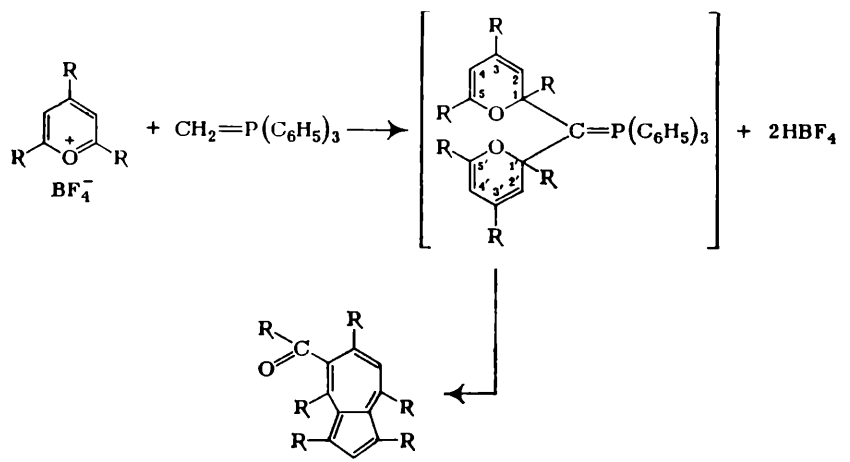


Another route is by the action of diazomethane on indane, the former being decomposed by exposure to ultraviolet light. The resulting cyclopentanoheptadiene is subjected to dehydrogenation over palladium (on charcoal) to give azulene:



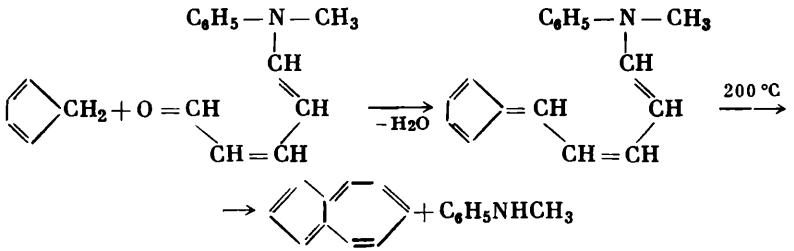
If appropriate conditions are chosen, it is possible to obtain azulene by the dehydrogenation, over palladium on charcoal, of cyclodecane (up to 50 per cent yield) or cyclodecene (yield up to 70 per cent).

In 1963 Dimroth, Wolff and Wache described a new route for synthesis of the azulenes—the action of excess triphenylphosphine-methylene (Wittig reagent) on pyrylium salts:

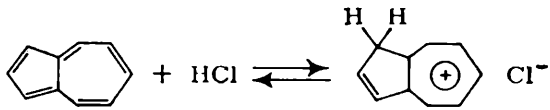


The yield of the product amounts to 30 per cent. The intermediate product given in square brackets is then protonated and the rings are opened with the formation of ketones; the carbonyl group in position 5′ condenses in the α-position 4 of the upper ring opened into a ketone, and the methylene carbon of the Wittig reagent splits off the triphenylphosphine, and becomes attached to carbon 4, closing the five-membered and seven-membered rings of azulene. With deficiency of the Wittig reagent the reaction proceeds in a different manner: the oxygen of the pyrylium salt is replaced by CH and the benzene ring is formed.

And, finally, the most practical pathway is the synthesis of azulene from pyridine (Ziegler). Pyridine is converted into a monomethylaniline derivative of the enol form of glutacondialdehyde, which condenses, at the expense of its second aldehyde group, with cyclopentadiene into the corresponding fulvene (Volume II, page 235). This fulvene when heated up to 200°C loses methylaniline and forms azulene in good yield:



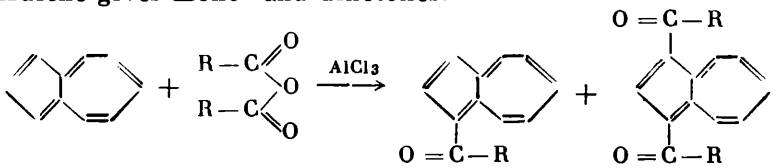
Azulene possesses weak basic properties; with acids it forms **azulenium salts**:



As a result of this reaction, the blue colour changes to yellow.

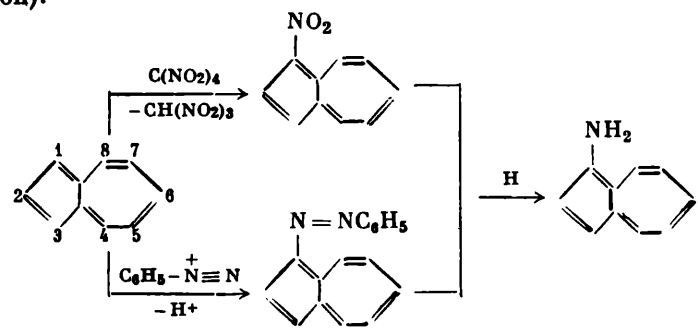
Azulene is an isomer of naphthalene and when heated up to 350°C and higher it is converted quantitatively into naphthalene which is more stable.

It is natural that azulene is capable of undergoing electrophilic substitutions in the five-membered ring. The Friedel-Crafts acylation of azulene gives mono- and diketones:



The alkylation of azulene proceeds in a similar way, though in low yield. Since azulene reacts with the hydrogen ion, it cannot be nitrated with nitric acid, but when azulene and alkylazulenes are allowed to react with tetranitromethane in pyridine solution, the nitration takes place in positions 1 and 3 (which are equivalent in azulene itself); 1,3-dinitroazulene has also been obtained. The sulphonation with a complex compound of sulphuric trioxide and dioxan or with a solution of sulphuric acid in acetic anhydride leads to the formation of 1,3-azulenedisulphonic acid. The monosulphonic acids of alkylazulenes have also been isolated. The positions 1 and 3 in azulene can also be halogenated with halogenosuccinimide.

Azulene readily undergoes azo coupling reactions under the action of the aryldiazonium cation (the scheme shows that the azo group enters the same position 1 of azulene as the nitro group upon nitration):



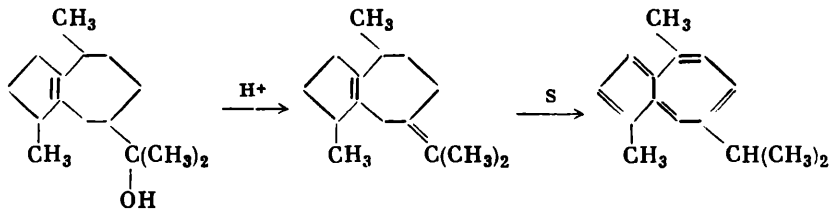
The action of a nucleophilic reagent, such as methyllithium, is directed to the positively charged seven-membered ring of azulene. Probably, first the addition of methyllithium across the double bond takes place so that the methyl group adds on to position 8 and the lithium adds to position 7 or 5. After hydrolysis there is formed 8-methyldihydroazulene which on dehydrogenation (with chloranil) is converted into 8-methylazulene (or, which is the same, 4-methylazulene).

As has been found relatively recently, azulene derivatives occur widely in the plant kingdom. Most of them are so-called **azulenogens** which belong to the class of sesquiterpenes (page 320) and have the molecular formula $C_{15}H_{24}$ (or their oxygen derivatives). For these compounds to be converted into azulene homologues, they must be dehydrogenated into $C_{15}H_{18}$. Such a dehydrogenation reaction is effected by heating with sulphur (200°C) or selenium (300°C), but the yield ranges from 5 to 30 per cent because at such high temperatures there takes place an isomerization to naphthalene derivatives. Dehydrogenation over palladium gives even lower yields.

The best dehydrogenating agent in this case is chloranil (tetrachloro-*p*-benzoquinone).

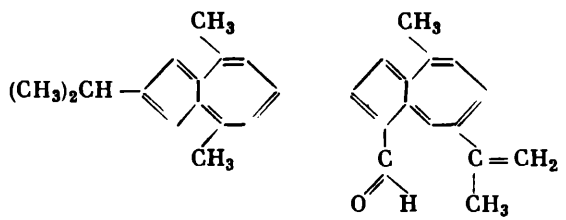
Sesquiterpenes having the azulene structure have been found in many essential oils and in plants, for example, in wormwood, carrots, vetiver, in the seeds of anise and dill (fennel), in yarrow and in saffron milk caps (*Lactarius deliciosus*).

An idea of the structure of these azulenic sesquiterpenes can be gained if we indicate that the principal constituent of the essential oil of the wood *Guaiacum officinale* is the sesquiterpenic alcohol guaiol, which on heating with acid is first dehydrated into guaiene and then converted by the action of sulphur into **guaiazulene**:

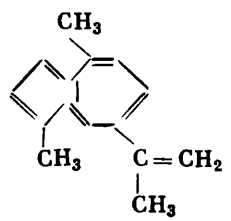


Guaiol Guaiene Guaiazulene

Vetivazulene, an isomer of guaiazulene, is prepared by dehydrogenation of the sesquiterpenic ketone β-vetivone which is contained in vetiver oil. The mushrooms saffron milk caps contain **lactaroviolin** and **lactarazulene**:



Vetivazulene Lactaroviolin



Lactarazulene

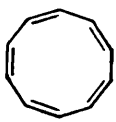
Bicyclo[0.3.3]octane does not undergo dehydrogenation, and other numerous attempts to synthesize pentalene have also failed. This hydrocarbon would contain not 6 and 10 but 8 electrons, form-

ing π-bonds:

The difficulty of its preparation points to its instability and hence its non-aromatic character. Aromatic properties are not displayed by **cyclooctatetraene** either, in which there are also only 8 π-electrons. Cyclooctatetraene, however, is capable of capturing two electrons (e.g., from metallic potassium) and being converted, as a result, into an aromatic dianion with 10π-electrons (Katz, 1960):

It has the ability to donate its two electrons to the molecules of various compounds and to be thus converted into electrically neutral cyclooctatetraene (D. N. Kursanov, Z. V. Todres).

The higher analogue of cyclooctatetraene, **cyclopentadecaene** has,



like cyclooctatetraene, the properties of an olefin, though it contains 10 electrons of π-bonds. This non-conformity with the Hückel rule is accounted for by the non-planarity of the ring, whereas for the orbitals of π-electrons to be overlapped continuously round the ring it is necessary (this condition is necessary but not sufficient) that the ring be planar or almost planar.

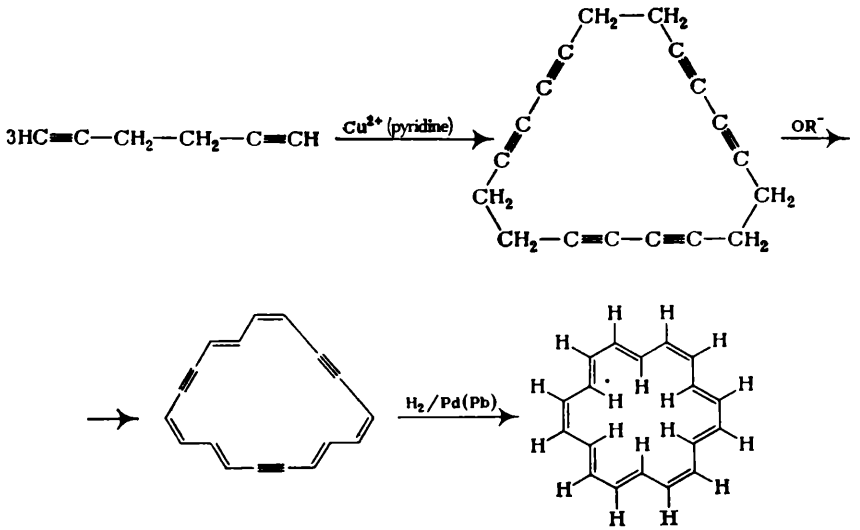
In **cyclododecahexaene**, $C_{12}H_{12}$, the number of π-bonds does not conform with the Hückel rule. Moreover, as can easily be seen, having taken into consideration the interatomic distances and the size of hydrogen atoms, in the configuration that could be planar (with alternating *cis*- and *trans*-arrangements round the olefinic bonds)

the hydrogen atoms in the centre of the molecule would have been overlapped and would not have enabled the molecule to assume a planar form.

Thus, a manifestation of aromatic properties might be expected from cyclopolyenes, C_nH_n, with the number of π-bonds equal to 7 (which corresponds to 14 electrons), 9 (18 electrons), 11 (22 electrons), etc., which may have a planar configuration. Cyclooctadecanonaene, $C_{18}H_{18}$ (an annulene), was prepared in 1959.

B. Annulenes

The annulenes are higher cyclic polyenes containing a fully conjugated system of π-bonds. Their synthesis may be exemplified by the synthesis of **cyclooctadecanonadiene** or [18]-annulene (Sondheimer), which has been prepared by the following series of reactions:



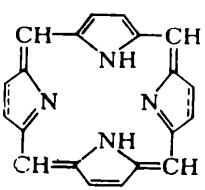
The first stage of the reaction proceeds with a yield of about 6 per cent to the side of formation of a cyclic polyene. The second stage is an ordinary migration of the π-bonds under the action of an alkaline reagent. The third stage is the hydrogenation of triple bonds over palladium poisoned by lead. This [18]-annulene, like other annulenes, has an all *trans*-configuration, so that its hydrogen atoms may be classed into two types: **peripheral** and **intra-annular** hydrogen atoms, which is clearly evidenced by the NMR spectrum (see Volume II, page 294). Under the influence of a variable magnetic field (precisely, its vector perpendicular to the plane of the aromatic ring) the π-electrons form a ring current which causes, in its turn, a relatively small vector of the magnetic field, which is opposite to the applied field and is directed away from the centre of the aromatic

molecule. This is the shielding effect which weakens the influence of the external field on the protons in the centre of the aromatic molecule, just as in [18]-annulene. Hence, a higher external field must be imposed in order to overcome this shielding effect and cause NMR. There takes place a chemical shift of the signal of the intra-annular protons to the side of high fields, even higher fields than for the ordinary standard—the protons of tetramethylsilane (by 1.9 ppm to the right).

On the contrary, the peripheral protons, just as in all ordinary aromatic systems, have a chemical shift in a weak field (at 8.8 ppm). This is accounted for by the fact that outside the aromatic ring the direction of magnetic force lines, as is always the case round the solenoid, is opposite to their direction inside the ring-solenoid and thus causes a deshielding effect.

C. Porphyrins

Heterocyclic aromatic systems with a planar form of the molecule and 18 π-electrons, which are known as **porphyrins**, are widely distributed in nature and have been produced synthetically. The parent compound is **porphin**



(the dashed lines stand for double bonds that do not participate in the conjugation system)

Porphin

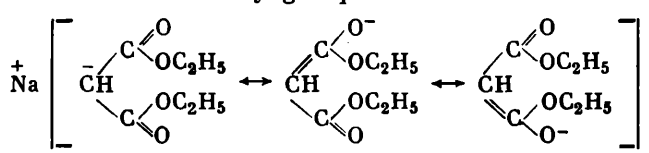
The porphyrin system forms the basic structural unit of chlorophyll present in the green leaves of plants and the red matter of blood—the haemoglobin. It is highly stable. (The chemistry of porphyrins has been discussed in Volume III, page 346.) A similar structure is shown by **phthalocyanins** prepared by heating the nitrile of phthalic acid and its derivatives with a copper salt (see Volume III, page 360).

In porphyrins and phthalocyanins the hydrogen atoms at two nitrogen atoms are readily replaced by various metals (magnesium, iron, copper), the metal atom being symmetrically linked via coordinative bonds to the other two nitrogen atoms.

Chapter 14

Carbanions

We have already encountered carbanions as intermediates in reactions of nucleophilic addition across the π-bonds of olefins. Other carbanion reactions have also been considered in the preceding volumes of this book. Examples are the action of alkyl halides on ionic sodium alkyls or sodium aryls; alkylation of sodium acetylide; alkylation of sodiomalonic ester; condensation reactions at the α-methylenic unit of ketones in the presence of bases, and many other important reactions leading to the formation of new carbon-carbon bonds. The sodium, potassium, etc., derivatives of alkanes, alkenes, alkynes, arenes are ion pairs and contain a true carbanion as the active component in synthesis. The organolithium, organomagnesium and other organometallic compounds, the reactions of which have already been discussed (page 19 *et seq.*), often have a covalent bond between metal and carbon and, though their reactions are similar in many respects to the reactions of organosodium and organopotassium compounds, they cannot be regarded as the reactions of true carbanions. Sodiomalonic ester and similar compounds are ionic compounds, but the anionic charge is delocalized over the oxygen atoms of carbalkoxy groups to such an extent



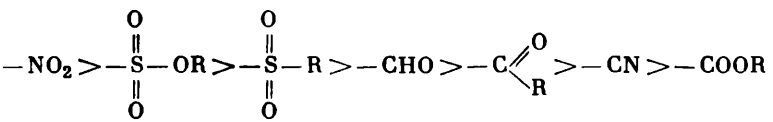
that we may speak of them as carbanions only conditionally.

There is some ground for naming them carbanions, namely, the fact that any electrophilic attack (for example, on alkylation by alkyl halides) still takes place at carbon. The anions of sodioacetoacetic ester and similar compounds may be regarded as carbanions with even more reservations since the anion in these compounds has undoubtedly the enolate structure with a greater part of the charge

on oxygen. However, in this case, too, in virtue of the transfer of the reaction centre the alkylation usually proceeds at the carbon atom. The aromatic analogue of the enolate, sodium phenoxide, cannot be regarded as belonging to substances containing a carbanion as a structural unit, though at least some of its alkylation reactions, say, allylation, also take place at carbon under certain conditions. Carboxylation with carbon dioxide in the Kolbe reaction also occurs at carbon.

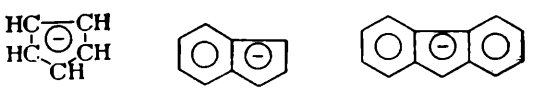
The hydrocarbon residue present in the molecule—methyl, methylene, or methine—becomes capable of forming a carbanion directly (losing a proton under the influence of bases) under the action of the electron-attracting group attached to this hydrocarbon residue.

Electron-attracting groups are arranged in the following sequence according to their tendency towards "acidification" (the tendency of the hydrogen atom of the methylene group attached to them to leave the molecule as a proton):



These electron-attracting groups, however, when accepting a greater or a considerable part of the anionic charge, thereby introduce some conditionality into the concept of the carbanion.

In certain carbanion structures, the distribution of the anionic charge is achieved without the participation of any of the electron-attracting groups given above; the stability of the carbanion is also achieved in this way even in certain protic solvents. Such are the cyclopentadienyl, indenyl, and fluorenyl anions:



In the cyclopentadienyl anion the extra electron that creates an anionic charge is involved in the aromatic sextet (see page 143) and belongs to the entire system of the aromatic five-membered ring, being equally distributed among the five carbon atoms.

The conversion of the hydrocarbon moiety of the molecule into a carbanion is effected by removal of a proton under the action of a base which is stronger than the resulting carbanion. Examples are the following:

$$C_6H_6 + \bar{C}_2H_5\,Na^+ \longrightarrow \bar{C}_6H_5\,Na^+ + C_2H_6 \text{ (Shorygin reaction)}$$

$$CH{\equiv}CH + NaNH_2 \longrightarrow NaC{\equiv}CH + NH_3$$

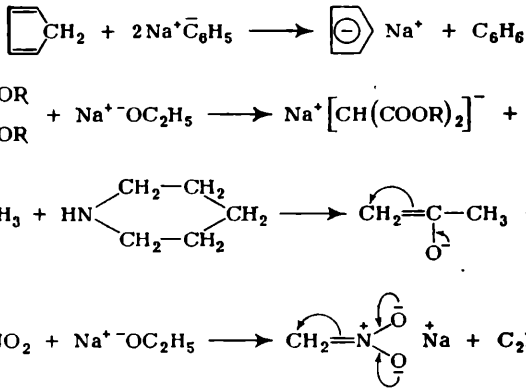


Table 14.1 presents pK_a values (after Cram) for a number of compounds (the values given are rounded off); those of weak acids have been estimated by indirect methods.

TABLE 14.1. The McEwen-Streitwieser-Applequist-Dessy (MSAD) Scale

Compound	pK_a	Compound	pK_a
Cyclopentadiene	15	Benzene	37
Indene	18.5	Tryptycene (α-position)	38
Phenylacetylene	18.5	Cyclopropane	39
Fluorene	22.9	Methane	40
Acetylene*	25	Ethane	42
Triphenylmethane	32.5	Cyclobutane	43
Toluene (α-position)	35	Neopentane	44
Propene (α-position)	35.5	Propane (*sec*-position)	44
Cycloheptatriene	36	Cyclopentane	44
Ethylene**	36	Cyclohexane	45

* According to the data obtained by Wooding and Higginson (*J. Chem. Soc.*, 1952, 774) and given on the MSAD scale.

** S. Miller and W. Lee [*J. Am. Chem. Soc.*, 81, 6313, (1959)] cite the value 34-36 for the upper limit of pK_a values of 1,2-dihaloethylenes.

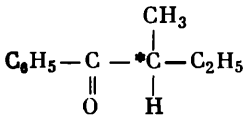
The constants K_a can be measured directly only for comparatively strong acids, those at the beginning of the table. For weaker acids use is made of the fact that the logarithm of the constant K_a of the equilibrium

$$RH \rightleftarrows R: + H^+$$

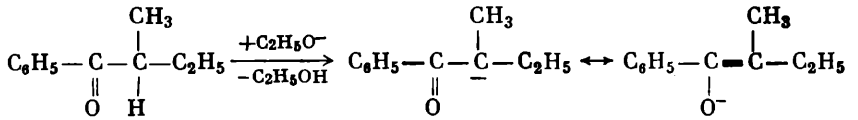
is linearly related to the logarithm of the dissociation rate constant in the same solvent and at the same temperature. Knowing this relationship, one can calculate the equilibrium constant from the data obtained by measurements of the ionization rate. The rate of ionization of RH can be measured from the rate of bromination (the bromination of the carbanion R: is an electrophilic reaction), from the rate of the isotope exchange reaction

$$RH \xrightarrow{D^+} RD + H^+$$

or, in certain cases, from the rate of racemization of R:, if the anionic charge is on the asymmetric carbon atom. Using the action of the alkoxide anion on the stereoisomer



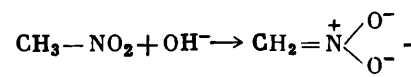
Ingold and Hughes showed (1936-1938) that the rates of all the three reactions (racemization, deuterium exchange, and bromination) coincide since the slowest (rate-determining) step of each of the processes is the interaction of a ketone with the alkoxide anion (i.e., expulsion of the proton from the α-position):

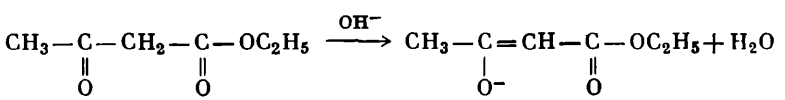


The only difference between this process and the dissociation of ordinary acids is that the former proceeds very slowly; the dissociation of acids also always involves a base in the Brönsted-Lewis sense, which may be exemplified by a trivial case:

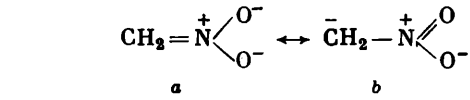
$$H-Cl + H_2O \rightleftarrows H_3O^+ + Cl^-$$

Acids that give carbanions of any type on dissociation are usually classed as pseudo-acids (which, according to Hantzsch, are compounds whose anion differs structurally from the parent pseudo-acid). The following are examples:

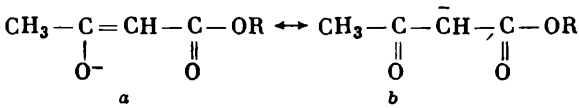




That we basically speak every time of a mesomeric ion



a *b*



a *b*

does not change anything since the contribution of the form *a* to the resonance structure of the mesomeric anion is so great that the form *b* may be neglected.

TABLE 14.2. **Logarithms of Dissociation Constants and Rates of Ionization and Recombination of Ions of True Acids and Pseudo-Acids**

Formula	pK	k_1	k_2	Formula	pK	k_1	k_2
H_2O	15.7	—4.6	11.1	CH_3COCH_3	20	—9.3	10.7
H_3BO_3	9.1	1.0	10.1	$CH_2(COOC_2H_5)_2$	13.3	—4.6	8.7
H_2SO_4	1.6	9.0	10.6	$CH_3COCH_2COCH_3$	9.0	—1.8	7.2
CH_3COOH	4.8	5.9	10.7	$C_2H_5NO_2$	8.6	—7.4	1.2
$CH_3COCOOH$	2.6	6.3	8.9	$CH_2(NO_2)_2$	3.6	—0.1	3.5

It is precisely pseudo-acids of the type that differ from ordinary (oxy-) acids by the slowness of ionization. Table 14.2 gives the rates of dissociation (k_1) and the reverse reaction (k_2)

$$HA + H_2O \underset{k_2}{\overset{k_1}{\rightleftarrows}} A^- + H_3O^+$$

for some true acids and pseudo-acids, and also their dissociation constants (presented as pK), equal to the k_1/k_2 ratio:

$$pK = \log k_2 - \log k_1$$

It is interesting that nitroethane is an acid which is much stronger than malonic ester but not because it rapidly dissociates into ions (on the contrary, it dissociates more slowly), but because the recombination of ions is strongly hindered for it (the value of k_2 is low; $\log k_2 = 1.2$).

In spite of what has been said above, for a large number of acids of the type there is an approximate correlation between K_a

and the rate of proton removal, the number of exceptions is so great that this cannot be considered to be a general rule. For example, no nitro compound fits into the scheme given (V. M. Belikov, 1965):

$$R_2CH + OH^- \rightleftarrows R_2\bar{C} + H_2O$$
$$\quad | \qquad\qquad\quad |$$
$$\quad NO_2 \qquad\qquad NO_2$$

The same situation is observed for the reverse reaction of protonation of carbanions. A lack of correlation (Fig. 14.1) is ascribed

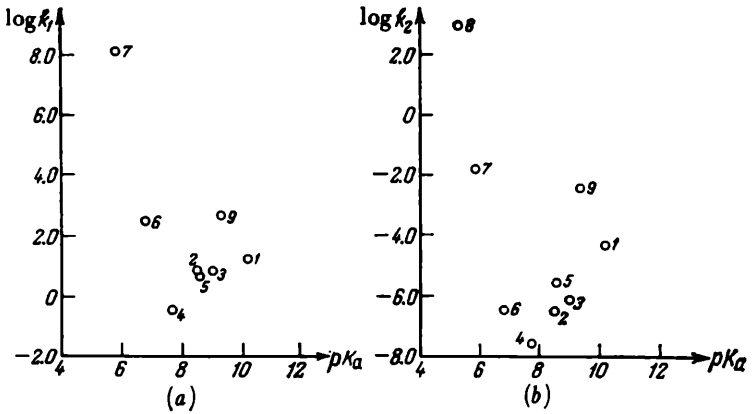


Fig. 14.1.

The rate constants (in $l \cdot mole^{-1} \cdot sec^{-1}$) of proton removal by OH^- ion (*a*) and protonation of carbanion by water (*b*) for a series of acids $RR'CHNO_2$ and their pK_a:

1—CH_3NO_2; *2*—$C_2H_5NO_2$; *3*—*n*-$C_3H_7NO_2$; *4*—*iso*-$C_3H_7NO_2$; *5*—*n*-$C_4H_9NO_2$; *6*—$C_6H_5CH_2NO_2$; *7*—$C_6H_7OCOCH_2NO_2$; *8*—$CH_2CH(NO_2)_2$; *9*—$C_6H_5CH(OH)CH_2NO_2$;

to the effect of internal (structure) and external (solvation) factors on the acidity of carbanions and on the rate of proton removal as they are formed (Fig. 14.1*a*)

$$RR'CH + OH^- \underset{k_2}{\overset{k_1}{\rightleftarrows}} RR'C^- + H_2O$$
$$\quad | \qquad\qquad\quad |$$
$$\quad NO_2 \qquad\qquad NO_2$$

The most important structural factor is the mesomeric effect of the substituent, which stabilizes the carbanion. More often than not the mesomeric and inductive effects of substituents act in the same direction, though there are exceptions, say, in the case of fluorine (I. L. Knunyants, 1964, Kamlet, 1966).

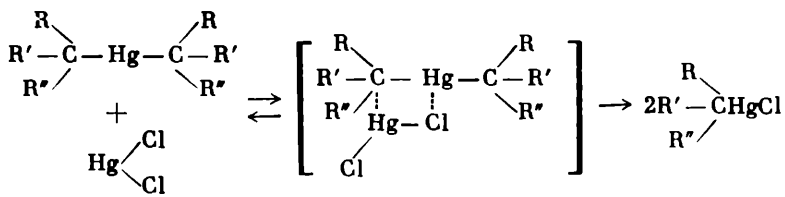
External factors (solvation) play a very important and, possibly, decisive part. On passing from water to aprotic solvents incapable of

stabilizing a carbanion due to hydrogen bonds, the following phenomena are observed: the dissociation constant decreases by 10 orders of magnitude, and the rate of dissociation sharply increases, reaching the values characteristic of O—H acids. According to Ritchie (1964), the last-named phenomenon is accounted for by the rebuilding of the solvation shell round the reacting molecules, which requires the major part of energy in reactions taking place in hydroxyl solvents. In aprotic solvents no such rebuilding is required. The formation of carbanions, especially from acids of the type RH, as has been said, invariably requires the participation of a base and proceeds as a slow reaction:

$$RH + B: \rightleftarrows R:^- + BH$$

If this is so, then it is obvious that any (preceding or following) process, faster than the formation of a carbanion, cannot be measured in kinetic experiments and the rate of the entire process is determined by this slow step. Since a large excess of B: is taken, the reaction is first order in RH (pseudomonomolecular) and any of carbanion reactions (bromination, racemization, deuterium addition, etc.) will also be a first-order reaction and will be designated as S_E1 (i.e., electrophilic substitution, first-order).

Reactions of the type S_E1 are contrasted to S_E2 reactions, which are electrophilic substitutions proceeding as reactions of second kinetic order, the rate of which is proportional to the concentration of RH and the concentration of the acting electrophilic reagent. Reactions of the type S_E2 proceed via a transition state in which the reacting molecules are bound, say, as follows:



In these reactions the asymmetric carbon atom—the centre of electrophilic attack—retains its configuration (O. A. Reutov).

The rate (and even the type) of the reaction is greatly influenced by the solvent. O. A. Reutov and I. P. Beletskaya succeeded in making a reaction of the type given above proceed by the S_E1 mechanism instead of by the S_E2 mechanism by replacing the solvent (alcohol with dimethyl sulphoxide), which is evidenced by the kinetics and racemization which follows the preliminary ionization of the organomercury compound.

Cram has found that the abstraction of a proton from a carboxylic acid RH by a base B: (e.g., by the alkoxide anion) in dimethyl sul-

phoxide takes place by 10^8 times faster than in methanol. This cannot be ascribed to the difference between the dielectric constants of the two solvents, which is relatively small. Cram attributed this to the solvation of the base by alcohol, which leads to the formation of the hydrogen bond $B\cdots H—O—CH_3$; for example:

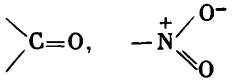
$$CH_3O^- + CH_3OH \longrightarrow [CH_3—O \cdots H—O—CH_3]^-$$

The solvation sharply weakens the nucleophilic properties of the base.

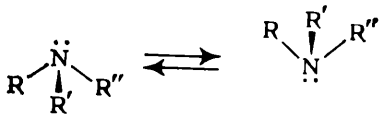
A particularly strong base is potassium *tert*-butoxide in dimethyl sulphoxide.

An example of racemization of a ketone with an asymmetric α-carbon atom, which involves the abstraction of a proton by a base with conversion of the ketone into the corresponding anion has been given above. This case, however, cannot be regarded as typical since the anion in question has undoubtedly the structure of the enolate anion, and the asymmetric tetrahedral sp^3-carbon atom changes to a carbon atom with an olefinic bond —with a planar trigonal configuration.

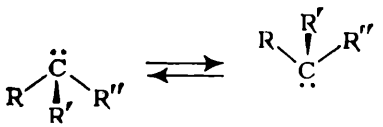
Such racemization is inevitable in all cases where the negative charge is not only delocalized but is rather concentrated on a group with oxygen (an electron acceptor) adjacent to the reaction centre. The following are examples of such groups:



By analogy with the absence of optical isomers in the case of tertiary amines of pyramidal structure having three different substituents

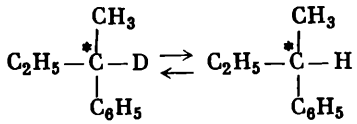


which may be explained by the pyramidal configuration being rapidly turned inside out, the existence of optical isomerism would also seem quite impossible for true carbanions for the same reasons:



In fact, however, cases of partial retention of configuration as well as those of partial inversion of configuration (i.e., partial racemization) have been observed in carbanion reactions.

Cram studied the rate of hydrogen-deuterium exchange reactions (the constant k_e) and the rate of racemization—the loss of rotation of the plane of polarization (the constant k_r) in reactions of the stereoisomer 2-deutero-2-phenylbutane with a base in various solvents:



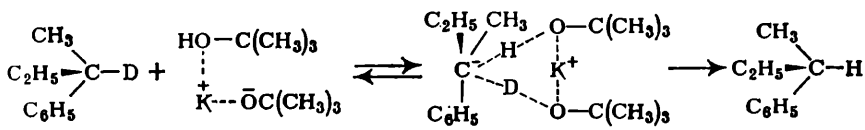
If the hydrogen-deuterium exchange proceeds with complete retention of configuration, with complete racemization, and with complete inversion of configuration, the following ratios must be observed, respectively: $k_e/k_r = \infty$, $k_e/k_r = 1$, and $k_e/k_r = 0.5$.

The experimental results are presented in Table 14.3. From the

TABLE 14.3

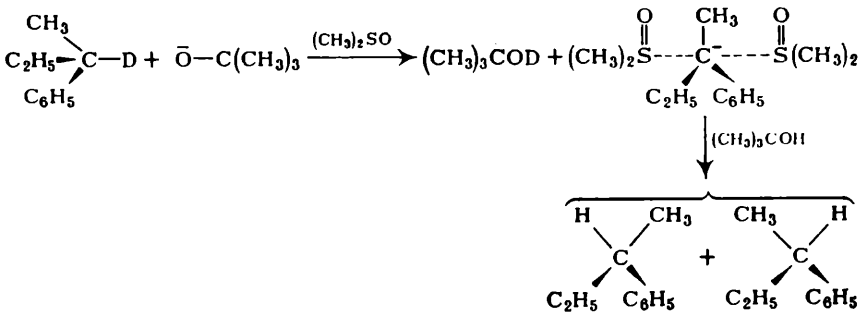
Solvent	Base	k_e/k_r	Stereochemical result
$(CH_3)_3COH$	$(CH_3)_3CO^-K^+$	10	Retention of configuration
$(CH_3)_2SO + (CH_3)_3COH$	$(CH_3)_3CO^-K^+$	1	Racemization
$O(CH_2CH_2OH)_2$	$HOCH_2CH_2OCH_2CH_2O^-K^+$	0.7	Inversion of configuration

data given it is clearly seen that the stereochemical course of the reaction is sharply influenced by the nature of the solvent. This can be explained as follows. In *tert*-butyl alcohol as a solvent, potassium *tert*-butoxide, though being ionized, does not dissociate into ions, i.e., it forms an ion pair which is not separated and is solvated by the solvent. This solvated ion pair attacks the stereoisomer 2-deutero-2-phenylbutane, abstracting the deuteron and supplying a proton in its place. All this takes place from one side of the carbanion, and the configuration is retained on deuterium exchange:

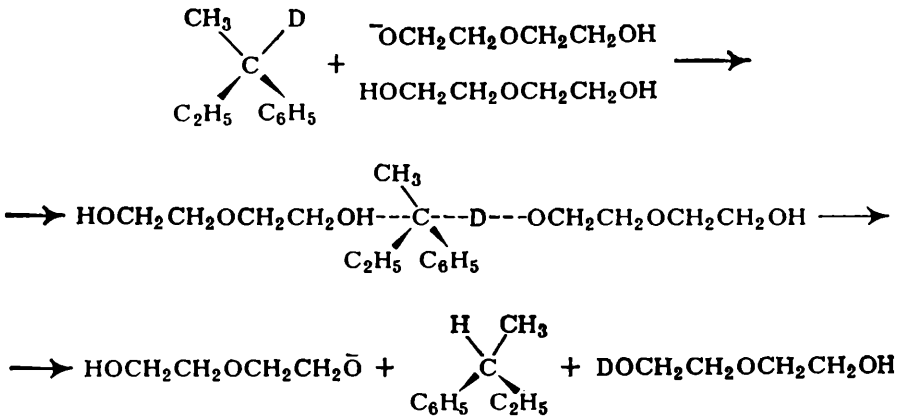


In dimethyl sulphoxide, the ion pair of potassium *tert*-butoxide is completely dissociated and the attack is accomplished by the *tert*-butoxide anion which splits off the deuteron. The resulting

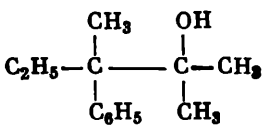
carbanion has ample opportunity to become planar before being attacked by the *tert*-butyl alcohol introduced in a small amount into the solvent from both sides of the plane. In virtue of this, the deuterium exchange reaction proceeds with racemization:



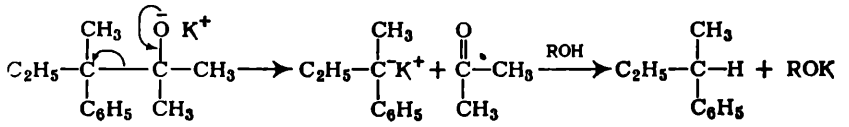
In diethylene glycol the ion pair of the alkoxide is well dissociated and the deuterium, just as in the previous case, is attacked by the alkoxide anion. But since diethylene glycol is a better proton donor than *tert*-butyl alcohol, the synchronous attack of the planar carbanion from the rear with a proton supplied is accomplished by the diethylene glycol molecule. The result is inversion of configuration (Walden inversion):



A similar case of the solvent action has been described by Cram for the cleavage (a reaction analogous to the reverse aldol condensation) of the alcohol



by a base with the formation of the same carbanion (the methylethylphenyl anion):



The stereochemical relations observed in this reaction are presented in Table 14.4.

TABLE 14.4

Solvent	Base	Stereochemical result
$(CH_3)_3COH$	$(CH_3)_3CO^-K^+$	Retention of configuration (90-99%)
$(CH_3)_3COH$	$(CH_3)_4\overset{+}{N}OH^-$	Racemization (100%)
$(CH_3)_2SO + CH_3OH$	$CH_3O^-K^+$	Racemization (100%)
CH_3OH	$CH_3O^-K^+$	Inversion of configuration (40-60%)

In *tert*-butyl alcohol which does not separate (does not cause dissociation of) the ion pairs and solvates the base, there is again observed retention of configuration for the reasons indicated above. However, in the same medium, tetramethylammonium hydroxide, a non-solvated cation, undergoes complete racemization. The same complete racemization occurs in dimethyl sulphoxide. On the contrary, in methanol, a solvent with strong dissociating properties, the attack is made by the methoxide anion, and a proton is supplied by methyl alcohol itself, which is an excellent proton-donor. The result is a high percentage of Walden inversion.

All the above-described reactions of formation of a carbanion as an unstable intermediate boil down to the removal of a proton (or, less often, a metal cation) from a carbon atom under the action of a base or a solvating solvent. Another route for the formation of a carbanion is also possible—the nucleophilic attack at a double carbon-carbon bond. However, not any carbon-carbon π-bond is capable of undergoing nucleophilic attack. For this to take place, it must be conjugated with an electron-attracting group, or carbon atoms bearing π-electrons must be directly attached to electron-attracting atoms or groups. Thus, systems of the following types can undergo nucleophilic attack by the anions HO^-, RO^-, $RCOO^-$, NH_2^- (and the corresponding derivatives), CN^- and by a number of

carbanions:

I $CF_2=CF_2$ $(CN)_2C=C(CN)_2$ $CF_3CH=CH_2$ $(CF_3)_2C=CH_2$ $(CF_3)_2C=CF_2$

II $CH_2=CH-\overset{\overset{O}{\|}}{C}-R$ $CH_2=CH-NO_2$ $CH_2=CH-C\equiv N$ $CH_2=CH-SO_2R$

III $R-\overset{\overset{O}{\|}}{C}-CH=CH-\overset{\overset{O}{\|}}{C}-R'$ $R-\overset{\overset{O}{\|}}{C}-CH=CH-NO_2$ $R-\overset{\overset{O}{\|}}{C}-CH=CH-C\equiv N$

$R-\overset{\overset{O}{\|}}{C}-CH=CH-SO_2R$

The reaction begins with the attack of the anion on the carbon atom whose partner being attached to it by a π-bond is capable of bearing the carbanion charge more firmly than the carbon atom being attacked:

$$X-\overset{1}{C}H=\overset{2}{C}H-Y+Z: \rightarrow X-\overset{\cdot\cdot}{C}H-\underset{\underset{Z}{|}}{CH}-Y$$

The carbanion formed as a result of the attack of the anion must thus be more stable (with a lower energy) than the isomeric carbanion. The stability of the carbanion is attained by the extensive delocalization of the negative charge over the contiguous groups. The ability of the adjacent groups to delocalize (i.e., take up partially) the charge of the carbanion decreases, according to Arndt and Eistert, in the following order:

$$-\underset{\underset{H}{|}}{C}=O > -\underset{\underset{R}{|}}{C}=O > -\underset{\underset{OR}{|}}{C}=O > C\equiv N$$

In reactions of this type the formation of a carbanion is the slowest step of the reaction, which determines its kinetic course. In a general form, represented by the equation given above, the group X delocalizes electrons better than the group Y (for example, if $X = CH_3-\overset{\overset{O}{\|}}{C}-$, and Y = CN). If X and Y are identical groups, then the attack takes place with equal probability on this or that olefinic carbon atom.

This is followed by the fast step of the reaction (which does not affect its kinetics)—the stabilization of the anion, which occurs by either of the two routes. The anion can be stabilized by way of addition of a proton from the medium which completes the process resulting in the addition of a molecule of AH to the double bond (where A^- is the anion initiating the reaction). The frequently encountered alternative stabilization is accomplished by the ejection from the molecule of a group of atoms attached to carbon in the form of

another anion which leads to the recovery of an unsaturated bond. The result of the reaction is a nucleophilic substitution.

Examples of nucleophilic addition are:

$$CCl_3-CH=CH-NO_2+CH_3O^- \longrightarrow$$

$$\longrightarrow CCl_3-\underset{\underset{OCH_3}{|}}{CH}-\bar{C}H-NO_2 \xrightarrow{CH_3OH} CCl_3-\underset{\underset{OCH_3}{|}}{CH}-CH_2-NO_2+CH_3O^-$$

$$CCl_3-CH=CH-NO_2+Cl^- \longrightarrow$$

$$\longrightarrow CCl_3-\underset{\underset{Cl}{|}}{CH}-\bar{C}H-NO_2 \xrightarrow{H^+} CCl_3-\underset{\underset{Cl}{|}}{CH}-CH_2-NO_2$$

$$CF_3-\underset{\underset{CH_3}{|}}{C}=CH-COOCH_3+RO^- \longrightarrow CF_3-\underset{\underset{CH_3}{|}}{\overset{\overset{OR}{|}}{C}}-\bar{C}H-\underset{\underset{O}{\|}}{C}-OCH_3 \xrightarrow{ROH}$$

$$\longrightarrow CF_3-\underset{\underset{CH_3}{|}}{\overset{\overset{OR}{|}}{C}}-CH_2-\underset{\underset{O}{\|}}{C}OCH_3+RO^-$$

$$C_6H_5\underset{\underset{O}{\|}}{C}-CH=CH-\underset{\underset{O}{\|}}{C}OH+RS^- \longrightarrow C_6H_5\underset{\underset{O}{\|}}{C}-\bar{C}H-\overset{\overset{SR}{|}}{C}H-\underset{\underset{O}{\|}}{C}OH \xrightarrow{RSH}$$

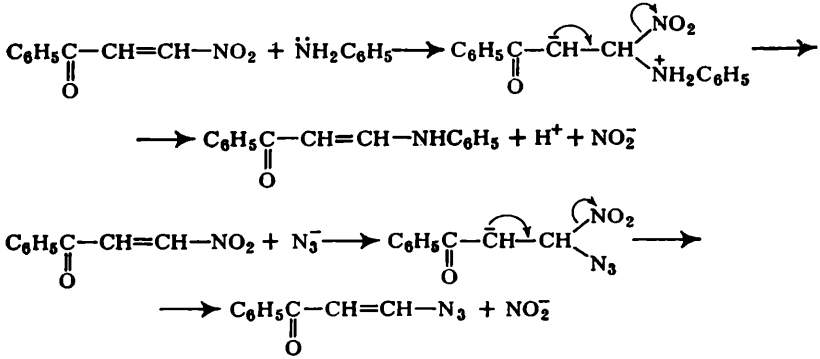
$$\longrightarrow C_6H_5-\underset{\underset{O}{\|}}{C}-CH_2-\overset{\overset{SR}{|}}{C}H-\underset{\underset{O}{\|}}{C}OH+RS^-$$

Examples of nucleophilic substitution proceeding via the stage of nucleophilic attack on π-bonds are as follows:

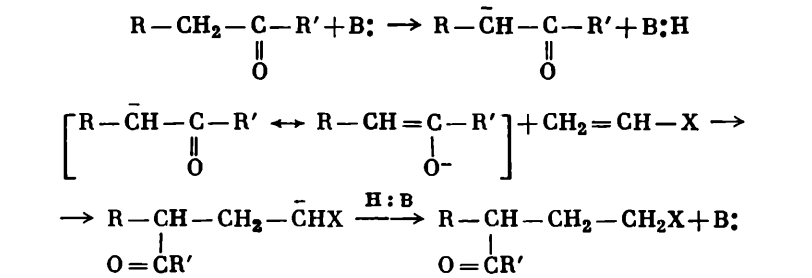
$$(NC)_2C=C(CN)_2 + CH_3O^- \longrightarrow (NC)_2\bar{C}-\overset{\overset{CN}{\curvearrowright}}{C}(CN)-\underset{\underset{OCH_3}{|}}{C}N \longrightarrow (NC)_2C=\underset{\underset{OCH_3}{|}}{C}(CN) + CN^-$$

$$RO_2S\diagdown C=C\diagup CN \quad NC\diagup \quad \diagdown SO_2R + CH_3O^- \longrightarrow RO_2S\diagdown \bar{C}-\overset{\overset{CN}{\curvearrowright}}{C}(SO_2R)-\underset{\underset{OCH_3}{|}}{C}N \longrightarrow$$

$$\longrightarrow RO_2S\diagdown C=C\diagup CN \quad NC\diagup \quad \diagdown OCH_3 + RSO_2^-$$

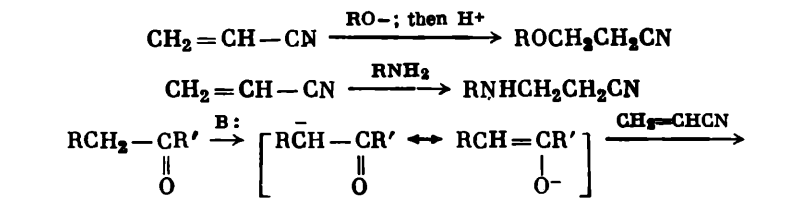


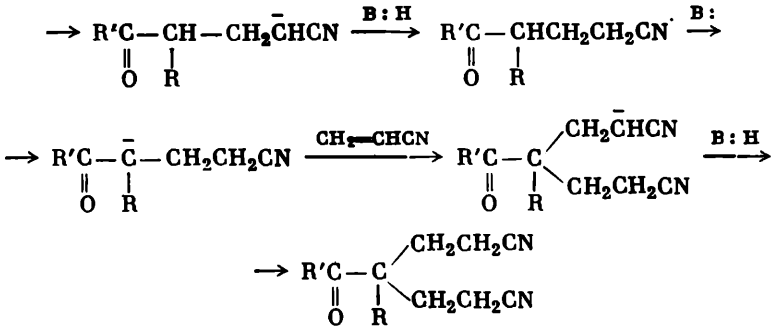
Especially interesting from the preparative standpoint are reactions of olefinic bonds, which are capable of taking up nucleophilic attacks, with carbanions. These include the Michael condensations, for example:



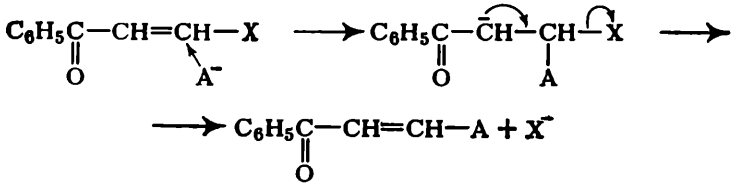
where X = $-\overset{\overset{O}{\|}}{C}-R$; $-NO_2$; $-CN$ or any other group that activates the carbon-carbon π-bond towards nucleophilic attack, i.e., an electron-withdrawing group.

A special case of reactions of acrylonitrile with carbanions and also with oxygen-containing and other anions is called the **cyanoethylation reaction.** This reaction discovered by Bruson has been especially thoroughly studied by A. P. Terentiev and A. N. Kost. The following are examples of cyanoethylation reactions:

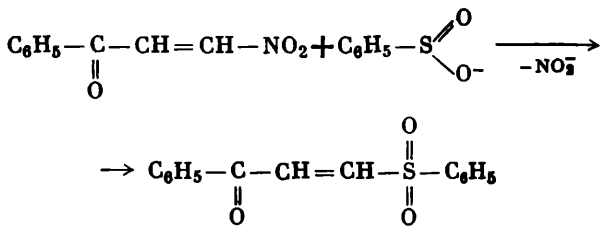




The reaction of addition of an anion to compounds of the type RCO—CH=CH—X, where X = Cl, CN, NO_2, etc., is often accompanied by the ejection of the anion X and, as has been said above, changes to nucleophilic substitution. This may probably occur in those cases when X is exactly the group that readily leaves as an anion:

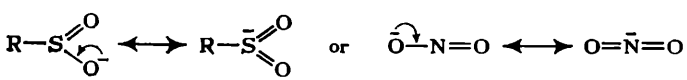


In this reaction A^- may be the anion of benzenesulphinic acid, which forms a sulphone*:



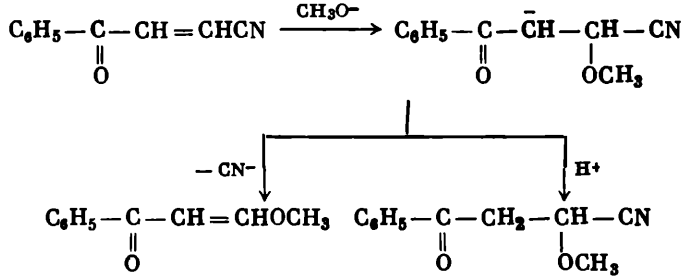
or the anion of hydrazoic acid, N_3^-. Reactions of this type, which have been thoroughly studied by A. N. Nesmeyanov, N. K. Kochet-

* The anion of sulphinic acid, like the nitrite anion, often reacts with a transfer of the reaction centre from O to S (or, accordingly, to N):

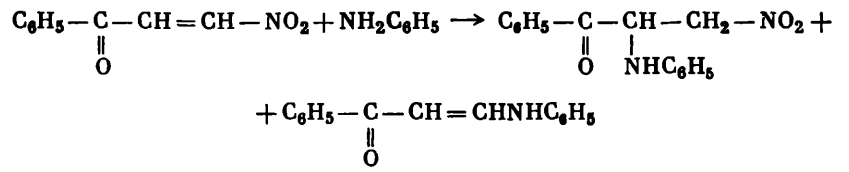


kov, M. I. Rybinskaya, and L. V. Rybin, are called **ketovinylation reactions.**

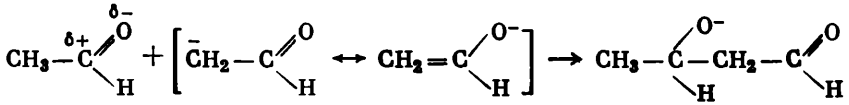
In other cases, where the C—X bond undergoes heterolysis more slowly (X = CN), two products (substitution and addition) can be isolated:



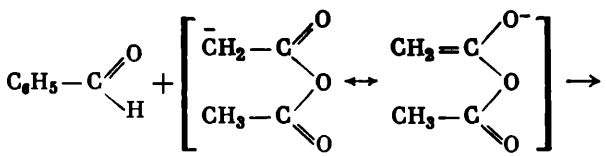
It is interesting that in the case of β-nitrovinyl ketones the dual orientation of nucleophilic attack has been detected. This is exemplified by the reaction with aniline:

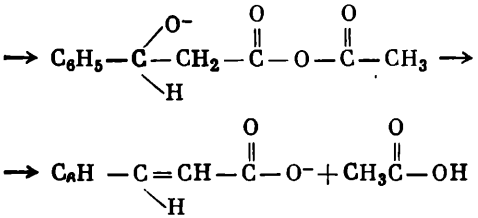


Finally, carbanions (in the most cases those generated by the action of bases) react with the positively charged carbon atom of the carbonyl group of aldehydes and ketones. These are the well-known reactions of addition at the carbonyl double bond of the anion of an aldehyde or ketone (aldol condensation)

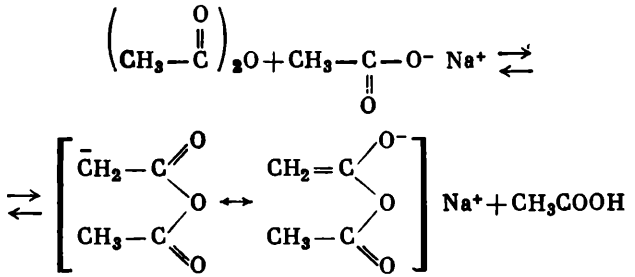


or of the anion of acetic anhydride (Perkin condensation):

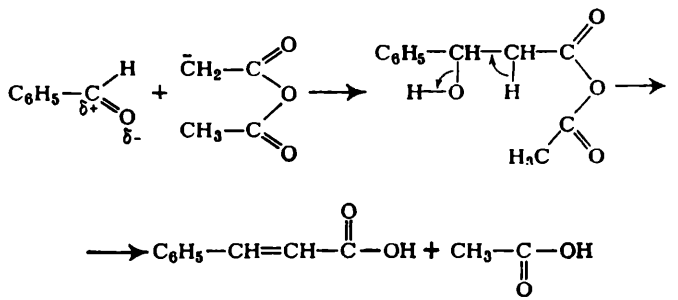




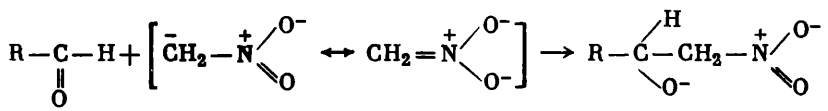
In the case of the Perkin condensation it may be assumed that the first step of the reaction is the formation of a small amount of the anion of acetic anhydride as a result of an exchange reaction with sodium acetate:



The second stage involves the attack of the mesomeric anion of acetic anhydride on the carbonyl carbon, condensation and then the elimination of water and the hydrolysis of the mixed anhydride:



Nitromethane adds on to aldehydes under the action of bases:



Such carbanion reactions generally play a very important part in synthetic chemistry. They also include well-known reactions,

such as the addition of hydrocyanic acid and of the acetylene anion $HC{\equiv}C^-$ to carbonyl compounds (A. E. Favorsky, W. Reppe).

Tetracyanoethylene which has already been mentioned is capable of completely withdrawing an electron, say, from metallic potassium or from the iodide ion, forming the radical-anion of tetracyanoethylene:

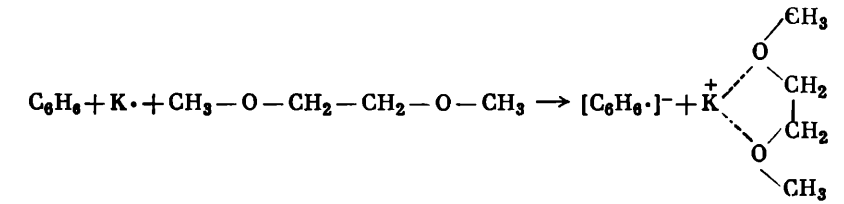
$$(NC)_2C{=}C(CN)_2 + K \longrightarrow K^+ + (NC)_2C{=}\dot{C}(CN)_2$$

$$2(NC)_2C{=}C(CN)_2 + 3KI \longrightarrow 2K^+ + 2\left[(NC)_2C{=}\dot{C}(CN)_2\right] + K^+I_3^-$$

The potassium salt of the tetracyanoethylene anion exists in the form of crystals having a bronze colour. The EPR spectrum* of this anion is split into nine lines.

Tetracyanoethylene is also capable of reacting with aromatic compounds, but with a partial transfer of an electron from the aromatic ring to tetracyanoethylene, so that both molecules are bound into a coloured paramagnetic complex. With durene (1,2,4,5-tetramethylbenzene) and condensed aromatic hydrocarbons such complexes can be obtained not only in solutions but also in the individual solid state. Similar complexes with a partial transfer of an electron are formed by quinones (see Volume III, page 188) with aromatic compounds.

Tetracyanoethylene and quinones are compounds possessing high electron affinity and therefore readily form radical-anions or complexes which are called **charge-transfer complexes.** Under certain conditions, however, radical-anions are also formed from aromatic hydrocarbons. Thus, benzene is reduced at a lower temperature by metallic potassium in a solution of dimethoxyethane with the formation of a radical-anion. In this reaction, dimethoxyethane plays an important part by solvating the potassium ion:



In the radical-anion of benzene, the extra electron is transferred to the first excited orbital π^* which embraces the entire system, so that its density is uniformly distributed over all the six carbon

* For EPR spectra, see Chapter 15.

atoms. Accordingly, the EPR spectrum shows seven lines of hyperfine structure with the following intensity ratio: 1:6:15:20:15:6:1.

In the analogously formed radical-anion of toluene the extra-electron density is distributed in a different way—over the *ortho*- and *meta*-carbon atoms of the ring, which gives five principal lines of the spectrum (V. V. Voevodsky, S. P. Solodovnikov).

It should be noted that **metal ketyls** obtained by reducing aromatic ketones with potassium or sodium

$$C_6H_5-\underset{\underset{O}{\|}}{C}-C_6H_5 + K\cdot \longrightarrow \left[C_6H_5-\dot{\underset{\underset{O^-}{|}}{C}}-C_6H_5\right] K^+$$

and so-called **phosphyls**, the products resulting from the reduction of oxides of tertiary phosphines, are also radical-anions. One example of phosphyls is

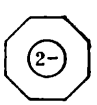
$$[(C_6H_5)_3\dot{P}-O^-]\ K^+$$

(M. I. Kabachnik, V. V. Voevodsky and coworkers).

Radical-anions can also be generated in reductions effected by other methods, say, by electrochemical reduction. It has been found recently that they play an important part in many reactions which begin with an electron transfer, say, in metalation reactions and particularly in biochemical reduction processes (L. A. Blumenfeld).

Radical-anions and charge-transfer complexes are usually intensely coloured compounds since the unpaired electron in them occupies the first excited orbital and may be transferred to the nearest-lying orbital, which corresponds to the absorption of a quantum of visible light.

It has been established recently that some unsaturated conjugated systems are capable of adding two electrons with the formation of doubly charged anions called **dianions**. An example is the cyclooctatetraene dianion studied by D. N. Kursanov and coworkers (page 168):

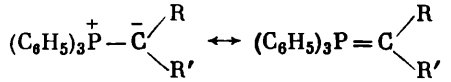


In such a dianion there is formed an aromatic sextet of electrons ($4n + 2$) and it is therefore stable.

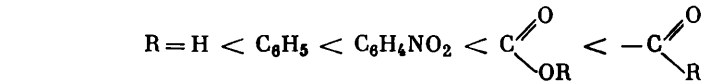
There also exist **radical-dianions** which are particles formed from aromatic carbanions to which one more electron is added.

A large group of carbanions is constituted by ylides of which the most important synthetically are phosphorylides (the Wittig reaction, see Volume I, page 335). These carbanions are bipolar ions in

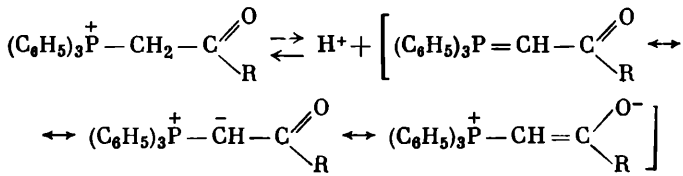
which the positive charge is localized on the onium atom, and the negative charge, to a greater or lesser extent, on carbon; for example:



Just as in other cases, the stability of these bipolar carbanions depends on the extent of delocalization of the anionic charge. Thus, in the phosphorylide series $(C_6H_5)_3\overset{+}{P}-\overset{-}{C}HR$ the stability increases in the following sequence:



Phosphorylides carrying a carbonyl group are so stable that the corresponding acylphosphoniums



are acids comparable in strength to carboxylic acids. According to the findings of M. I. Kabachnik and T. A. Mastryukova, the triphenylphenacylphosphonium salts $[(C_6H_5)_3\overset{+}{P}CH_2COC_6H_5]X^-$ are acids with a dissociation constant of $pK_a = 6.5$ in 50 percent alcohol; the pK_a value of benzoic acid in 50 percent alcohol is 5.63.

Chapter 15

Free Radicals

Reactions proceeding via the stage of formation of free radicals have been mentioned in various places in this course. Examples are: chlorination and bromination reactions in the light (Volume I, page 92); sulphochlorination in the light (Volume I, page 94); oxidation by molecular oxygen (Volume I, page 343, and Volume III, page 164); thermal cracking of hydrocarbons (Volume I, page 91); decomposition of some azo and diazo compounds (Volume III, page 124); radical polymerization (Volume I, page 346) and telomerization reactions (page 217).

Most of these reactions proceed by a chain mechanism (Volume I, page 93).

Free radicals under discussion may be of the following types: (a) unstable (thermodynamically) particles—fragments of molecules with an unpaired electron, such as $CH_3\cdot$ and $C_6H_5\cdot$ and their homologues; (b) atoms having an unpaired electron, say, H·, Cl·, Na·; (c) and, finally, there exist thermodynamically stable radicals, such as triarylmethyl radicals (Volume III, page 248) and semiquinones whose stability is attained by the delocalization of the unpaired electron over π-conjugated (in this case, aromatic) structures. The oxides of nitrogen (NO_2, NO) are also stable free-radical particles since they have an unpaired electron.

The unpaired electron of the hydrogen atom is an *s*-electron; in the case of the chlorine atom and also any C-radical this is a *p*-electron.

A stable free radical does not usually enter into exchange reactions with a molecule and only unites with a radical. Therefore such radicals cannot propagate the chain but can terminate it (since they remove free radicals which are chain carriers) and thus serve as chain-reaction inhibitors. Some compounds of transition metals contain unpaired electrons on *d*-levels. These are quite stable compounds which do not exhibit the reactivity of free radicals, but

are sometimes capable of generating a free radical by withdrawing an electron and of initiating a chain reaction.

All these particles and molecules with unpaired electrons are paramagnetic owing to the uncompensated spin of the electron, which can be established by means of magnetic balances (as far as stable particles are concerned) or by electron paramagnetic resonance measurements (including unstable particles in reactions if the concentration of free radicals is not too low).

15.1. Electron Paramagnetic Resonance

The electron paramagnetic resonance (or electron spin resonance) method discovered by E. K. Zavoisky in Kazan in 1945 has become a powerful tool for identification of free radicals and for observation of the behaviour of unpaired electrons in molecules. This method is based on the following. In an imposed constant magnetic field H the unpaired electron can orient itself either in the direction of the applied field or against the direction of the field. The two orientations define two energy states, which differ in energy of the electron. This energy difference E is given by the formula:

$$E = g\beta H$$

where g is a constant quantity equal to 2.0023 for a free electron; β is the Bohr magneton equal to 0.927×10^{-20} erg/gauss.

Such splitting of the energy levels of the electron in the magnetic field makes possible the absorption of energy E by the electron in the lower energy state, as a result of which the electron moves to a higher state. This is attained by subjecting a free radical present in a constant magnetic field H to short-wave radiation $h\nu = E = g\beta H$. It is at the wavelength of this radiation, which is determined by the given relation, that **resonance absorption** takes place.

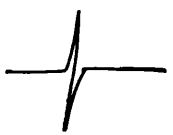
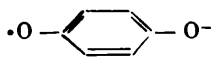


Fig. 15.1.
The EPR spectrum of a free radical.

The method is highly sensitive and enables free-radical concentrations up to 10^{-12} mole/litre to be detected. The absorption curve has a form with a sharply prominent peak (Fig. 15.1). Such a simple form of the curve is however obtained only if a radical contains no atomic nuclei having a spin (and, hence, a magnetic moment) and capable of interacting with the unpaired electron. Since a proton has a spin, the most ordinary case is the presence of such an interaction, which is called the **spin-spin splitting.** In this process the only peak changes to $(n + 1)$ peaks where n is the number of identically positioned

hydrogen atoms interacting with the unpaired electron. For instance, for the methyl radical $n = 3$ and the absorption curve shows four peaks; for the hydroxyl radical HO• there evidently appear two peaks; for the semiquinone ion



in which the electron is delocalized over both oxygen atoms and all the four hydrogen atoms are symmetrical, i.e., $n = 4$, there are five peaks in the EPR spectrum. The picture is much more complicated if there are non-equivalent hydrogen atoms. It is however the spin-spin splitting that allows free radicals to be identified correctly from an individual EPR pattern characteristic of each free radical.

Another, older classical method of detecting unpaired electrons and, in particular, free radicals is spectroscopy. An unpaired electron reveals itself in the triplet nature of the corresponding spectrum line, so that the triplet and the free-radical state of the particle have come to be known as synonyms. Use is also made of mass spectroscopy. Since free-radical reactions most often proceed by a chain-type mechanism, use is made of measurements of the characteristic kinetics of chain reactions (see page 219) with their S-shaped course, including the initial induction period. The presence of free radicals is also deduced from the inhibition of chain reactions by addition of inhibitors—"radical catchers".

As we have seen in the case of the semiquinone ion, from EPR measurements there follows quite unambiguously a conclusion as to the objective reality of delocalization of a free electron over complex conjugated systems. Analogously, the EPR spectrum of the triphenylmethyl radical unambiguously shows that the unpaired electron of this radical interacts with all the 15 hydrogen atoms of the three phenyl nuclei.

15.2. The Formation of Free Radicals

All free-radical reactions begin with the formation of a free radical and therefore we shall dwell briefly on the methods of generation of free radicals.

We shall describe four types of reactions involving the formation of free radicals, which proceed predominantly in the gas phase or in a solvent having a low dielectric constant and a low solvating power. In solvents of high dielectric constant and high solvating power, heterolytic and ionic reactions predominate.

Type I. The homolysis of bonds, say, C—C, O—O, C—N= N, C—M (M = metal), which is effected by the following methods:

(a) pyrolysis, occasionally at low (e.g., room) temperatures, as for $(C_6H_5)_3C-C(C_6H_5)_3$, or at temperatures above 100°C, as for peroxides or the azodinitrile of isobutyric acid;

(b) irradiation (with ultraviolet quanta or hard radiation).

The energies required for the cleavage of various types of bonds are given in Volume I, page 433.

Type II. Reactions proceeding by the principle "a radical generates a radical", for example,

$$RCl + Na\cdot \longrightarrow R\cdot + NaCl$$

$$CH_3\cdot + CH_3CH_2CH_3 \longrightarrow CH_4 + CH_3-CHCH_3$$

$$CH_4 + Cl\cdot \longrightarrow CH_3\cdot + HCl$$

$$R\cdot + CH_2=CH_2 \longrightarrow RCH_2-CH_2\cdot$$

and so on.

Type III. Reactions with the participation of redox systems, in which an unpaired electron appears as a result of the transfer of one electron by a molecule with paired electrons to an oxidizing agent (usually, to the cation of a metal of variable valency) or, in some cases, of the reverse reaction:

$$ROOH + Co^{3+} \longrightarrow ROO\cdot + Co^{2+} + H^+$$

$$ROOH + Co^{2+} \longrightarrow RO\cdot + OH^- + Co^{3+}$$

$$ROOH + Fe^{2+} \longrightarrow RO\cdot + OH^- + Fe^{3+}$$

Type IV. Electrode processes, for example, of the Kolbe reaction type

$$R-\underset{\underset{O}{\|}}{C}-O^- - e \longrightarrow R-\underset{\underset{O}{\|}}{C}-O\cdot \longrightarrow R\cdot + CO_2$$

or the electrolysis of a Grignard reagent:

$$RMgX + e \longrightarrow R\cdot + Mg + X^-$$

Reactions of Type I. 1. The first reaction of this type, in which the formation of free methyl and ethyl radicals was proved, was the pyrolysis of vapours of tetramethyl lead and tetraethyl lead carried out by Paneth in 1929:

$$(C_2H_5)_4Pb \longrightarrow 4C_2H_5\cdot + Pb$$

The existence of methyl radicals in a rapid current of rarefied hydrogen (2 mm Hg) was proved by conversion of the metals Hg, Pb, Sn into their methyl derivatives. Knowing the velocity of the gaseous current carrying the radicals and the distance at which the interaction with the metal stopped, it was possible to calculate the life-time of the radicals, which was found to be of the order of

0.01 sec. The radicals gradually recombined

$$2CH_3\bullet \longrightarrow CH_3-CH_3$$

and disproportionated:

$$2C_2H_5\bullet \longrightarrow C_2H_4+C_2H_6$$

Other organometallic alkyl and aryl compounds behave in the same manner.

Such homolysis of organometallic compounds can also be accomplished photochemically, as has been demonstrated by G. A. Razuvaev, who was one of the first researchers of organic free-radical reactions in solutions as far back as the thirties of this century.

2. The pyrolysis of aliphatic hydrocarbons in liquid and gaseous phases (cracking) at a temperature of about 500-700°C leads to the fission of carbon-carbon bonds, which are less stable towards homolysis (84 kcal/mole) than carbon-hydrogen bonds (100 kcal/mole). Once the methyl or ethyl free radicals are detached they initiate a chain reaction: they abstract a hydrogen atom from new alkane molecules, preferably the tertiary, then the secondary and, finally, the primary hydrogen atom. The activation energy of abstraction of the primary hydrogen atom by a free radical is 2 kcal higher than that of the secondary, and 4 kcal higher than that of the tertiary hydrogen atom, at the same pre-exponential factor which corresponds to the reaction rate ratio at 500°C:

$$\text{primary : secondary : tertiary} = 1:3.7:13.4$$

The resulting new alkyl radical rapidly decomposes according to a scheme similar to the following one (a monomolecular reaction):

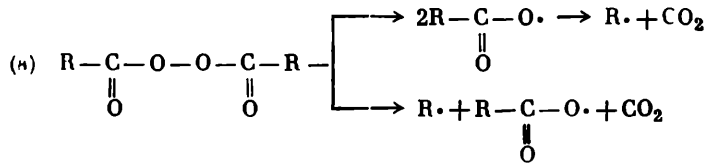
$$CH_3\bullet + C_nH_{2n+2} \longrightarrow CH_4 + \bullet C_nH_{2n+1}$$

$$CH_3-CH_2-CH_2-CH_2-CH-CH_3 \longrightarrow CH_3-CH_2-CH=CH_2 + \cdot CH_2CH_3$$

Only the methyl and ethyl radicals do not decompose under the cracking conditions. Thus, the radical (longer than the ethyl radical) left after the elimination of methyl or ethyl in the primary act of cracking, also decomposes and the reaction continues. Moreover, the radical may undergo isomerization. If the radical has a chain of six or more carbon atoms, it may isomerize, splitting off a hydrogen atom from one of its carbon atoms (usually, from position 5), as a result of which the radical centre is transferred to the energetically most favourable position, following which the radical decomposes homolytically. These relationships have been established by Rice who devised, on their basis, a method for quantitative calculation of the yield of cracking products.

3. The pyrolysis of peroxides takes place at relatively low temperatures (about 100°C). The pyrolysis may result in the formation

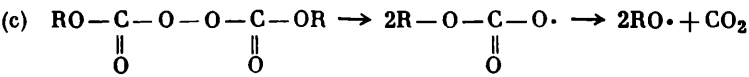
of either aliphatic or aromatic radicals R•:



(b) $(CH_3)_3C-OOH \longrightarrow (CH_3)_3CO\bullet + \bullet OH$

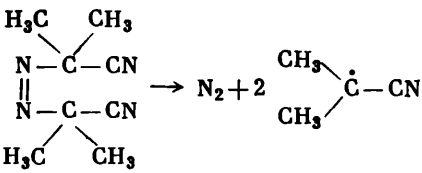
$(CH_3)_3CO\bullet + (CH_3)_3COOH \longrightarrow (CH_3)_3COH + (CH_3)_3C-OO\bullet$

$2(CH_3)_3C-OO\bullet \longrightarrow 2(CH_3)_3CO\bullet + O_2$

(c) 

Peroxydicarbonate

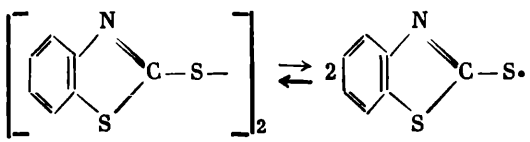
4. The pyrolysis of unstable azo compounds, say, of the azodinitrile of isobutyric acid:



5. The decomposition of aromatic diazo compounds in non-polar media:

$$Ar-N=N-Cl \longrightarrow Ar\bullet + N_2 + Cl\bullet$$

6. The molecule of disulphides, R—S—S—R, more or less readily dissociates into two radicals RS•. The ease of dissociation depends on the ability of R to delocalize the unpaired electron, so that the most favourable are aromatic and heterocyclic residues with a system of π-bonds, which reaches the carbon atom bearing S•. Such a compound is 2,2-benzthiazolyl disulphide which even at 100°C dissociates according to the following scheme with an equilibrium constant of 6×10^{-5}:



All reactions of type I can be used for initiation of the various chain reactions, reactions 3 and 4 being especially suitable in practice.

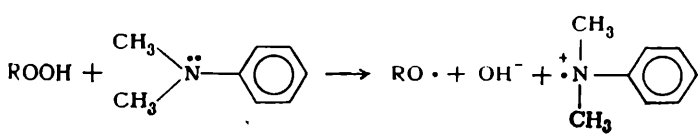
Reactions of Type II. The formation of free radicals from other radicals has already been discussed. Such reactions take place, as secondary reactions of further conversion, concurrently with any, especially high-temperature reactions of primary formation of free radicals. Numerous further examples of this kind will be encountered in the discussion of reactions involving decomposition and addition of free radicals.

Many molecules capable of thermal homolysis are found to be able to undergo photohomolysis (photodissociation) but the region of light absorption differs from compound to compound. Thus, peroxides absorb light at wavelengths below 3200 Å and are therefore unsuitable for photolysis in the glass. The azodinitrile of isobutyric acid absorbs light at any wavelength in the range 3450-4000 Å and is suitable for preparation of free radicals by photolysis. Dimethylmercury and tetraethyl lead undergo photodissociation under the influence of light at a wavelength of 2800 Å. The C—Hal bond in alkyl halides readily undergo homolysis under the action of light. For alkyl iodides to undergo homolysis, light with a wavelength of 3130 Å is required, and light of shorter wavelength is needed for the homolysis of alkyl bromides and chlorides to be effected.

Particularly thoroughly investigated is the photodissociation of acetone and other ketones (Noyes, Norrish) which proceeds according to the scheme:

$$CH_3-\underset{\underset{O}{\|}}{C}-CH_3 \longrightarrow CH_3\cdot + CH_3-\underset{\underset{O}{\|}}{C}\cdot$$

Reactions of Type III. As regards the generation of free radicals in redox systems, examples involving the ions of Mn, Co, and Fe of various oxidation states have already been cited. In such systems, a metal ion, while gaining or donating an electron, converts a molecule with an even number of electrons into a free radical with an unpaired electron or into a combination of a radical with an unpaired electron and an ion (or molecule) with an even number of electrons. There exist, however, redox systems which play the same role without the participation of a metal ion, say, peroxide-amine systems:



Redox systems of any kind are employed in practice as chain-reaction initiators, especially for polymerization in aqueous medium (emulsion polymerization).

15.3. Free-Radical Reactions

A. Elementary Acts

1. Accepting an electron, a free radical is converted into an anion. The electron affinity is expressed by the following values (in the gaseous phase):

Radical	Electron affinity, kcal/mole	Radical	Electron affinity, kcal/mole
Cl·	88.2	HO·	50
F·	83.5	C_6H_5O·	27
Br·	81.6	$(C_6H_5)_3C$·	48
I·	74.6	CH_3·	25
HOO·	70		

II. While giving an electron, a free radical forms a cation. Waters was the first to draw the conclusion that organic free radicals and the corresponding anions and cations form the couples of thermodynamically reversible oxidation-reduction systems:

$$R\cdot \rightleftarrows R^+ + e \qquad e + R\cdot \rightleftarrows R:^-$$

Rocci and Mog report evidence proving that 2-cyano-2-propyl radicals $CH_3-\dot{C}(CN)-CH_3$ reduce cupric salts in the acetonitrile medium by a one-electron transfer mechanism:

$$CH_3-\dot{C}(CN)-CH_3 + Cu^{2+} \longrightarrow CH_3-\overset{+}{C}(CN)-CH_3 + Cu^+$$

$$CH_3-\overset{+}{C}(CN)-CH_3 \xrightarrow{H_2O} \begin{cases} CH_3-C(=O)-CH_3 + H^+ + HCN \\ CH_2=C(CN)-CH_3 + H^+ \end{cases}$$

A radical which upon loss of an electron gives a relatively stable cation is called an **electron-donor radical.** Such radicals include alkyls, α-arylalkyls, α-hydroxyalkyls, acyls and α-aminoalkyls.

A radical which acquires an electron and gives a relatively stable anion is called an **electron-acceptor radical.** Examples are: polyhaloalkyl, α-cyanoalkyl, α-carbonyl and α-alkoxy radicals. The donor-acceptor properties of such radicals and the corresponding compounds

capable of forming the radicals indicated are manifested in the transition state of the reaction.

III. A reaction involving the union of two free radicals, either identical or different, which is called the **recombination**, does not require (or requires little) activation energy and is an ordinary reaction of chain termination in chain reactions. Examples are:

$$Cl\cdot + Cl\cdot \longrightarrow Cl_2 \quad \text{Chain termination in chlorination}$$

$$R\cdot + Cl\cdot \longrightarrow RCl$$

$$C_2H_5\cdot + H\cdot \longrightarrow C_2H_6 \quad \text{Chain termination in cracking}$$

$$CH_3\cdot + CH_3 \longrightarrow C_2H_6$$

$$RO\cdot + \cdot OR \longrightarrow ROOR \quad \text{Chain termination in oxidation reactions}$$

$$R-\overset{\overset{O}{\|}}{C}\cdot + R-\overset{\overset{O}{\|}}{C}-O\cdot \longrightarrow R-\overset{\overset{O}{\|}}{C}-O-\overset{\overset{O}{\|}}{C}-R$$

IV. Decomposition of Radicals. (a) Alkyl radicals higher than $C_2H_5\cdot$ are unstable under the conditions of pyrolysis (i.e., at temperatures of about 500°C) and break down according to the following scheme:

$$RC_nH_{2n}\cdot \longrightarrow R\cdot + C_nH_{2n}$$

Judging by the photochemically initiated homolytic substitutions of hydrogen in alkanes by chlorine, $-SO_2Cl$, etc. (page 201 *et seq.*), radicals $\cdot C_nH_{2n+1}$ with a long chain of carbon atoms are involved as intermediates in reactions at relatively low temperatures and do not decompose.

(b) Alkoxyl free radicals are able to decompose to give carbonyl compounds and alkyl free radicals:

$$(CH_3)_3C-O\cdot \longrightarrow (CH_3)_2C=O + CH_3\cdot$$

(c) Acyl radicals can decompose (at a higher temperature) into alkyl free radicals and carbon monoxide:

$$R-\overset{\overset{O}{\|}}{C}\cdot \longrightarrow R\cdot + CO$$

(d) Carbalkoxy radicals are highly unstable; they decarboxylate, forming alkyl (or aryl) free radicals:

$$R-\overset{\overset{O}{\|}}{C}-O\cdot \longrightarrow R\cdot + CO_2$$

(e) Peroxide radicals of the type $R-O-O\cdot$ are probably capable of decomposing as follows:

$$2R-O-O\cdot \longrightarrow 2R-O\cdot + O_2$$

though the following mechanism is not excluded:

$$2R-O-O\cdot \longrightarrow R-O-O-R + O_2$$

If the peroxide radical has an α-hydrogen atom, another process of decomposition is possible:

$$2R_2CH-O-O\cdot \longrightarrow R_2C=O+R_2CHOH+O_2$$

V. Reactions involving the intramolecular rearrangement of free radicals will be discussed in Chapter 20.

VI. *Disproportionation reactions*, i.e., reactions involving the conversion of two alkyl radicals (not lower than ethyl radicals) into a mixture of an alkane and an alkene. Such reactions, as shown by experiments with labelled ethyl $CH_3CD_2\cdot$ produced by the photolysis of $CH_3CD_2COCD_2CH_3$, proceed according to the "head-to-tail" mechanism:

$$CH_3-CD_2\cdot + H-CH_2-CD_2\cdot \longrightarrow CH_3-CD_2H+CH_2=CD_2$$

The presence of an unpaired electron in the radical weakens the surrounding bonds. For example, for $\cdot CH_2CH_2-H$ the bond energy is 40 kcal/mole, while for CH_3CH_2-H it is 98 kcal/mole.

VII. The reaction with oxygen is an ordinary step in a chain reaction of oxidation of hydrocarbons, aldehydes, ethers, etc., by oxygen:

$$R\cdot + O_2 \longrightarrow R-O-O\cdot$$

A radical with an odd electron on carbon is converted into a radical with an odd electron on oxygen.

VIII. Reactions with hydrogen- or halogen-containing molecules are an important special case of reactions proceeding by the principle of radical generation by a radical. In these reactions the free radical abstracts a hydrogen or halogen atom from the molecules of the medium, giving rise to a new free radical. Such reactions often constitute a step in a chain reaction, say, in oxidation reactions effected with oxygen. The isomerization of radicals is also possible (see page 302).

The following are examples:

$$R-\overset{\overset{O}{\|}}{C}-O-O\cdot + R-\overset{\overset{O}{\|}}{C}-H \longrightarrow R-\overset{\overset{O}{\|}}{C}-O-O-H+R-\overset{\overset{O}{\|}}{C}\cdot$$

$$R-\overset{\overset{O}{\|}}{C}-O-O\cdot + CH_3-\underset{\underset{OH}{|}}{CH}-CH_3 \longrightarrow R-\overset{\overset{O}{\|}}{C}-O-O-H+CH_3-\dot{\underset{\underset{OH}{|}}{C}}-CH_3$$

$$C_6H_5\cdot + C_2H_5OH \longrightarrow C_6H_6+CH_3\underset{\underset{OH}{|}}{C}H\cdot$$

$$C_6H_5\cdot + CH_3-\overset{\overset{O}{\|}}{C}-CH_3 \longrightarrow C_6H_6+CH_3-\overset{\overset{O}{\|}}{C}-CH_2\cdot$$

$$CCl_3\cdot + CH_3-\underset{\underset{OH}{|}}{CH}-CH_3 \longrightarrow CHCl_3 + CH_3-\underset{\underset{OH}{|}}{C}-CH_3$$

$$C_6H_5\cdot + CCl_4 \longrightarrow C_6H_5Cl + CCl_3\cdot$$

$$Cl + RH \longrightarrow HCl + R$$

$$R\cdot + SO_2Cl_2 \longrightarrow RCl + \cdot SO_2Cl$$

Hydrogen atoms are abstracted by radicals from aliphatic compounds but not from aromatic rings. For the behaviour of aliphatic unsaturated compounds, see Volume I, page 335 *et seq.*, and for that of aromatic compounds, see page 206 in this volume. The halogens are abstracted by hydrocarbon radicals from polyhalogen aliphatic compounds (in the case of chloroform, the hydrogen atom is preferably abstracted).

It is natural that radicals with an odd electron on oxygen abstract hydrogen and not halogen.

IX. Reactions of addition of free radicals to olefins

$$R\cdot + CH_2=CH_2 \longrightarrow R-CH_2-CH_2\cdot$$

generate homologous free radicals and are the first step of homolytic addition, telomerization, and radical polymerization reactions.

15.4. Free-Radical Chain Reactions

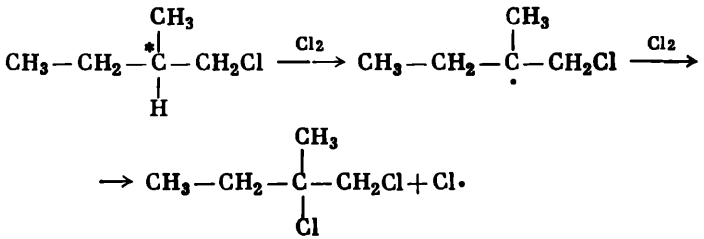
A. Homolytic Substitution

Halogenation. 1. A homolytic halogenation (fluorination, chlorination, and bromination) reaction can be effected by an elemental halogen in the light by a chain reaction mechanism. Table 15.1 gives the heats of the individual steps of the chain reaction of photochemical halogenation of methane (X_2 is the halogen molecule). Here $-\Delta H$ is, as always, the energy evolved in an exothermic reaction in the gas phase.

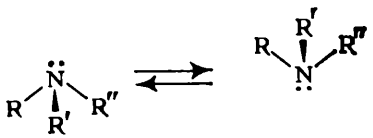
TABLE 15.1. **Heats of Individual Steps of the Halogenation of Methane ($-\Delta H$ kcal/mole)**

	F	Cl	Br	I
(*a*) $X_2 \xrightarrow{h\nu} 2X\cdot$	+37	+58	+46	+36
(b) $X\cdot + CH_4 \longrightarrow CH_3\cdot + HX$	−33	−1	+15	+31
(c) $R\cdot + X_2 \longrightarrow RX + X\cdot$	−60	−23	−21	−17
The sum $b+c$	−93	−24	−6	+14

As seen from Table 15.1, only fluorine and chlorine atoms abstract hydrogen from methane exothermally. With bromine, though the entire process is slightly exothermic, the stage of conversion of methane into the methyl radical is endothermic and the reaction fails to proceed. The situation is different in the photochemical bromination of alkanes—the homologues of methane—and cycloalkanes, but the reaction chains are also very short here and the quantum yields are low. For example, the quantum yield of the bromination of cyclohexane at room temperature is about 2, while that of chlorination, about 10^4, and the yield of fluorination even higher. The photochemical bromination of toluene into the chain is exothermic even at the stage of hydrogen abstraction because of the higher stability of the benzyl radical (and of its lower energy, a consequence of the delocalization of an electron over the conjugated π-electron system), and the reaction takes place. As has been demonstrated by Kharasch and Brown, the free-radical chlorination of optically active 1-chloro-2-methylbutane



leads to racemic 1,2-dichloro-2-methylbutane. This is a general rule—free radicals centre on the asymmetric carbon atom undergo racemization. Possibly, this happens due to the planar structure of the free radical or else, being pyramidal in structure, it is racemized owing to the same **tunnel effect** that excludes the existence of optical antipodes for tertiary amines of pyramidal structure, such as



The relative reactivities of hydrogen atoms in the radical chlorination of various hydrocarbons may be illustrated by the following comparison (100°C, the gas phase, the same reaction time):

CH_3	CH_2CH_3	$CH_2-CH-CH_3$		$CH_2C(CH_3)_3$	$CH_2-C(CH_3)_2$	
H	H	H	H	H	H	H
100	111	108	462	88	85	590

The number 100 is assumed to be the reactivity of the carbon-hydrogen bond in methane. The figures express the yield of a given chloro derivative, divided by the number of hydrogen atoms of the same species as the one being replaced (corrected for the statistical factor). In accordance with the high stability of tertiary and secondary free radicals as compared with primary ones, the substitution at the tertiary carbon occurs more rapidly than at the secondary and, especially, at the primary carbon. Methane is the most inert.

In a photochemical chlorination reaction taking place in solvents capable of forming a π-complex with Cl·, the difference in the rates of chlorination at the primary, secondary, and tertiary positions can be sharply increased. For instance, the relative reactivities of the primary and secondary hydrogen atoms towards chlorine at 25°C in *n*-pentane, benzene, and carbon disulphide (used as solvents) are, respectively, in the following ratios: 1:3, 1:5, and 1:29.

Electron-withdrawing groups slow down the homolytic chlorination. For example, the relative reactivities of α-, β-, and γ-linkages in butyric acid and propionitrile are expressed by the following figures:

$$\begin{array}{lll} \mathrm{C-C-C-C-OH} & & \mathrm{C-C-C\equiv N} \\ \quad 1 \quad 3 \quad 0.24 \quad \| \mathrm{O} & & \quad 1 \quad 0.5 \end{array}$$

2. Another method of homolytic chlorination (Kharasch) involves the action of sulphuryl chloride on hydrocarbons when the chain reaction is initiated by a peroxide. The series of reactions involved may be expressed by the following scheme:

$$\left(\mathrm{C_6H_5-\overset{\overset{\|}{\mathrm{O}}}{\mathrm{C}}-O}\right)_2 \longrightarrow 2\mathrm{C_6H_5-\overset{\overset{\|}{\mathrm{O}}}{\mathrm{C}}-O\cdot} \longrightarrow 2\mathrm{C_6H_5\cdot} + 2\mathrm{CO_2}$$

$$\mathrm{RH + C_6H_5\cdot \longrightarrow C_6H_5-H + R\cdot}$$

$$\mathrm{R\cdot + SO_2Cl_2 \longrightarrow RCl + \cdot SO_2Cl}$$

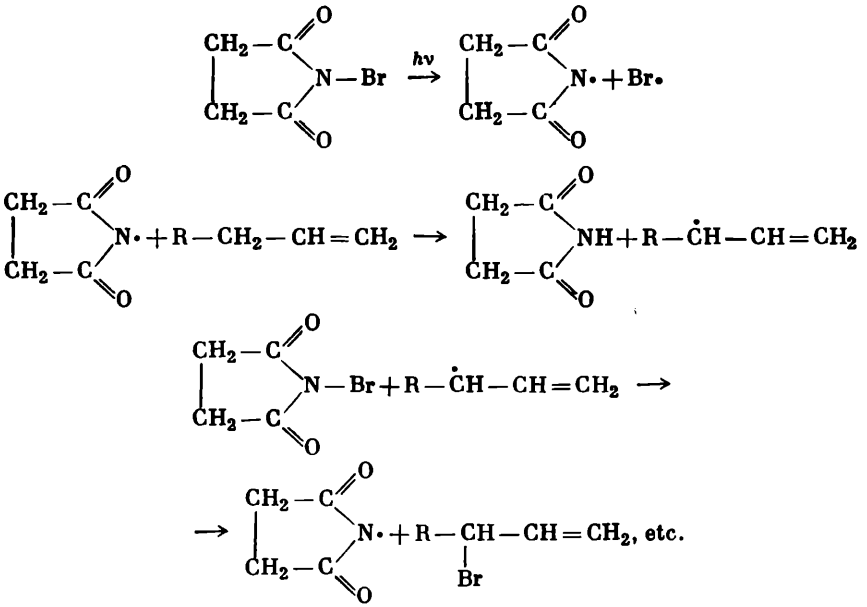
$$\mathrm{\cdot SO_2Cl \rightleftarrows SO_2 + Cl\cdot}$$

$$\mathrm{RH + \cdot SO_2Cl \longrightarrow R\cdot + HCl + SO_2}$$

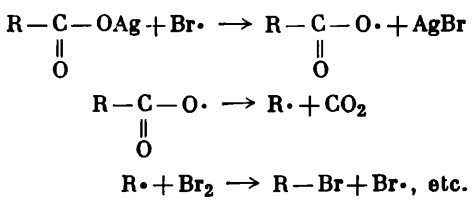
$$\mathrm{RH + Cl\cdot \longrightarrow R\cdot + HCl}, \text{ etc.}$$

Homolytic bromination is effected by means of bromosuccinimide. Homolytic chain reactions involving bromosuccinimide occur only in media of low dielectric constant or by the action of solid bromosuccinimide. Bromosuccinimide acts either on addition of a peroxide initiator, or under the influence of light, or else on heating. Of particular importance is the bromination into the allylic position, which

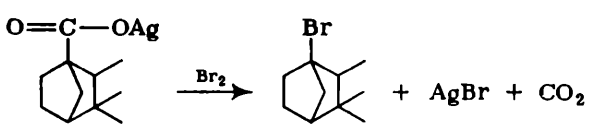
eaves the double bond intact. The reaction proceeds as follows:



3. The homolytic bromination and chlorination reactions can be accomplished by the action of halogen on a silver salt of a carboxylic acid (the Borodin-Hunsdiecker reaction). In this reaction, the initially formed acyloxy radical decarboxylates and the halogen atom occupies the place of the carboxyl group:



A specific feature of the reaction is that the halogen can be introduced in this way at the bridgehead of bicyclic systems, which cannot be achieved by any other nucleophilic substitution reaction: the replacement of any group X at the bridgehead by a nucleophile requires a Walden inversion (Volume II, page 50), which is impossible at the bridgehead in the rigid system of a bicyclic compound.



Thus, this is a special case of retention of configuration by a free radical.

Sulphochlorination. When an alkane is allo ed to react with sulphur dioxide and chlorine on illumination, a chain reaction takes place, which is employed to produce surface-active salts of alkanesulphonic acids (detergents):

$$Cl_2 \xrightarrow{h\nu} 2Cl\bullet$$

$$RH + Cl\bullet \longrightarrow R\bullet + HCl$$

$$R\bullet + SO_2 \longrightarrow R-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}\bullet$$

$$R-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}\bullet + Cl_2 \longrightarrow R-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-Cl + Cl\bullet$$

In this reaction a normal alkane is sulphochlorinated in the primary and in the secondary position (predominantly in the secondary position).

The same reaction can be effected by the action of sulphuryl chloride on an alkane in the presence of pyridine since the latter causes the decomposition of SO_2Cl_2:

$$SO_2Cl_2 \xrightarrow{\text{pyridine}} SO_2 + Cl_2$$

Chloroformylation. Upon irradiation oxalyl chloride and phosgene act on saturated hydrocarbons by the following chain reaction:

$$(COCl)_2 \xrightarrow{h\nu} 2\cdot C(=O)Cl \longrightarrow Cl\bullet + CO + \cdot C(=O)Cl$$

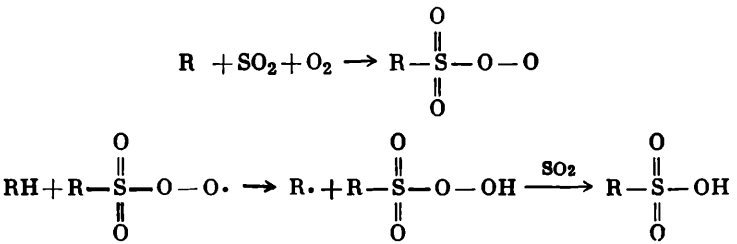
$$RH + Cl\bullet \longrightarrow R\bullet + HCl$$

$$R\bullet + (COCl)_2 \longrightarrow R-C(=O)Cl + \cdot COCl$$

$$\cdot COCl \longrightarrow CO + Cl\bullet$$

Introduction of the Sulpho Group. The sulpho group can be introduced by the action of O_2 and SO_2 on alkanes and cycloalkanes. The

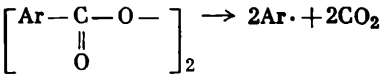
reaction proceeds under the influence of ultraviolet rays:

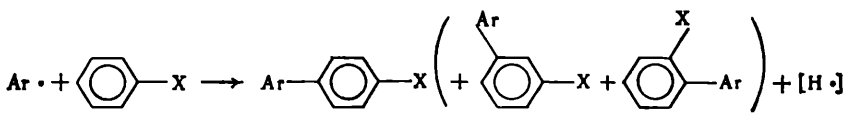


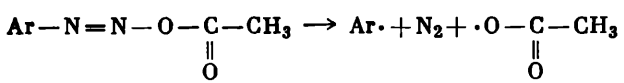
An analogous reaction is the reaction of alkanes with phosphorus trichloride and oxygen (L. Z. Soborovsky). The overall equation is as follows:

$$RH + PCl_3 + {}^1/_2O_2 \longrightarrow R-POCl_2 + HCl$$

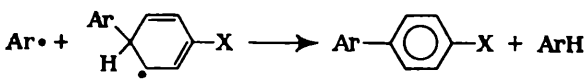
Homolytic Substitution in the Aromatic Ring. The most thoroughly studied reactions of this type are the arylations of benzene and its derivatives by means of free aryl radicals produced by the decomposition of aroyl peroxide or an aromatic diazo compound (the Gomberg-Bachmann reaction, 1924, see Volume III, page 126). It has been found (Hey) that the result of such arylation reactions is the same, regardless of the source of the aryl radical. The reaction proceeds according to the following schemes:







As a matter of fact, the hydrogen atom being replaced is probably not evolved in the free state but is eliminated by a second free radical from the σ-complex (Volume III, page 49) formed by the first free radical and an aromatic compound:



The intimate mechanism of this substitution stage cannot be elucidated by the investigation of only the kinetic and reaction

products, but it is clear that no chain reaction mechanism is involved at this stage and, hence, the hydrogen atom does not separate into the solution as a free radical.

Of the utmost interest in this connection is the orienting effect of substituent X in the benzene ring being attacked (Table 15.2).

As seen from the data given in Table 15.2, the substitution orientation in homolytic phenylation reactions is much less selective than in an electrophilic attack: all the three isomeric X-substituted derivatives of biphenyl are formed in comparable quantities. The difference in the orienting effect of the NO_2 and CH_3 groups is not too great, which means that the free phenyl radical has neither marked electrophilic nor nucleophilic activity. The situation may change if greater electrophilicity is imparted to the attacking free phenyl radical by introducing, say, the nitro group into it. In the case of the inductively electron-withdrawing group CCl_3 the situation changes sharply and CCl_3 behaves as a 100 per cent *meta*-directing group. But if the substituent in the aromatic compound being attacked is NO_2 or Cl, the situation does not change. Moreover, if phenyldiazoacetate is decomposed in an equimolar mixture of nitrobenzene and toluene, the amount of nitrodiphenyls obtained in the mixture is 4 times greater than that of methyldiphenyls, i.e., nitrobenzene reacts more vigorously than toluene. It may be assumed that the decisive factor here is the greater ability of the nitro group to delocalize an unpaired electron in the transition state and to decrease thereby the energy level of the transition state and the σ-complex upon attack at the *para*- or *ortho*-position relative to the nitro group. For example,

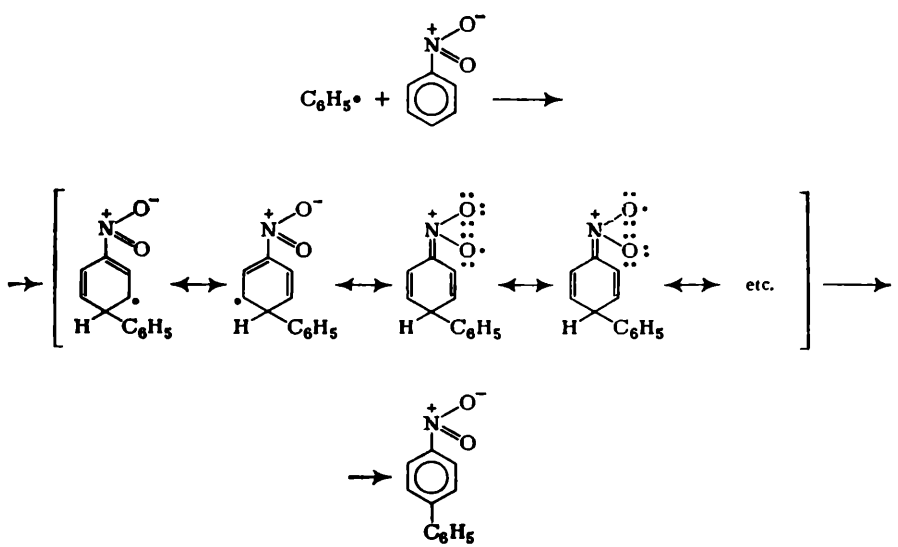
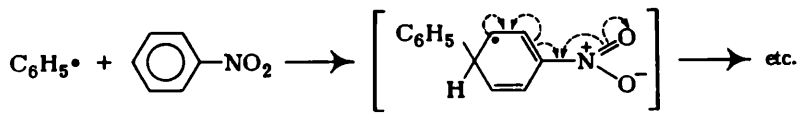


TABLE 15.2. **The Orienting Effect of Substituent X in the Benzene Ring in Homolytic Substitution by an Aryl (Radical Attack)**

Substituent X	Percentage content of isomers in the reaction product			Substituent X	Percentage content of isomers in the reaction product			Substituent X	Percentage content of isomers in the reaction product		
	ortho-	*meta-*	*para-*		*ortho-*	*meta-*	*para-*		*ortho-*	*meta-*	*para-*
	Attacking radical* $C_6H_5\cdot$							Attacking radical p-$NO_2C_6H_4\cdot$			
NO_2	62	10	28	CH_3	67	11	14	NO_2	58 [a]	15	27
F	54	31	15	C_2H_5	53	28	19	Cl	60	24	16
Cl	50	32	18	C_3H_7	31	42	27	CCl_3	0	100	0
Br	49	33	18	$(CH_3)_3C$	24	49	27				
I	52	32	17	C_6H_5	48.5	23	28.5				
CN	60	10	30	CF_3	29	41	30				
				CCl_3	12	49	39				

* The action of benzoyl peroxide at 80°C.

or, expressing the σ-complex by a single formula (the dashed arrows signify one-electron shifts):



The inductively acting groups CH_3, CCl_3, etc., cannot provide such an electron delocalization. The ability of the nitro group in the benzene ring to delocalize an odd electron follows from the greater homolytic dissociation of hexanitrophenylethane into triarylmethyl radicals as compared with hexaphenylethane (see Volume III, page 262).

B. Autoxidation Reactions

Autoxidation reactions are chain reactions of oxidation by molecular oxygen. They proceed as a result of the formation of free radicals due to the action of an initiator. The role of the initiator can be played by deliberately introduced radicals, the ions of metals of variable valency (Fe, Mn, Co, etc.), and, at elevated temperatures, by molecular oxygen itself, which is a diradical as evidenced by its paramagnetic properties and the triplet spectrum. With molecular oxygen the reaction proceeds as follows:

$$RH + O_2 \longrightarrow R\cdot + HO-O\cdot \qquad (1)$$

$$HO-O\cdot \longrightarrow HO\cdot + \cdot O\cdot \text{ (chain branching)}$$

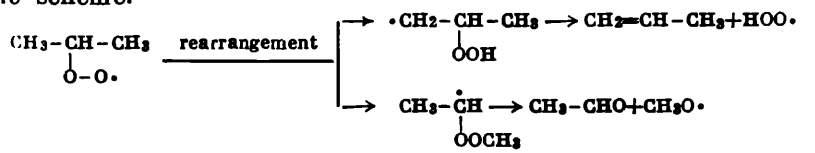
$$R\cdot + O_2 \longrightarrow ROO\cdot \qquad (2)$$

$$RH + ROO\cdot \longrightarrow ROOH + R\cdot \text{ etc.} \qquad (3)$$

$$ROO\cdot + R\cdot \longrightarrow ROOR \text{ (chain termination)} \qquad (4)$$

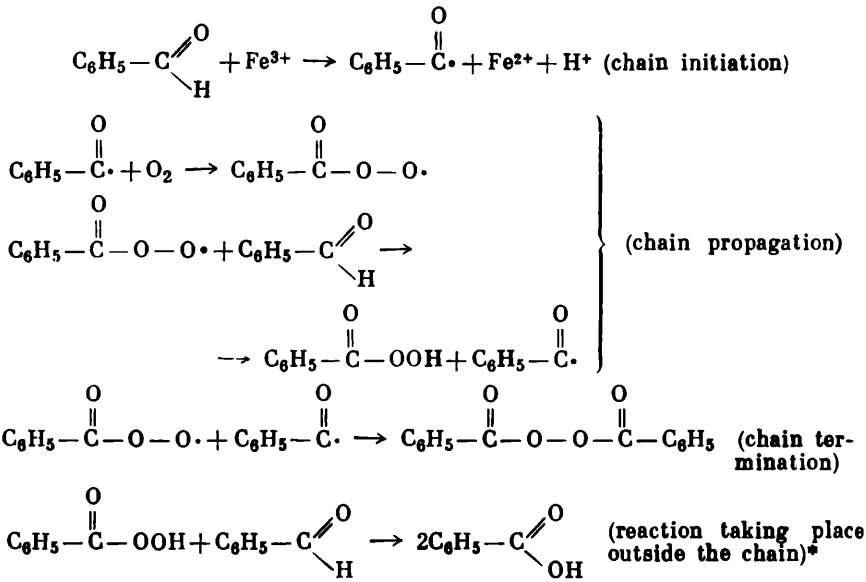
Stages 2 through 4 take place also in the case of formation of radical R· by the action of a foreign initiator.

At much higher temperatures the main products of the oxidation of saturated hydrocarbons are olefins, aldehydes, etc., whose formation is accounted for (N. N. Semenov) by the rearrangement of radicals ROO· followed by their decomposition, for example, according to the scheme:



An example of autoxidation is the familiar (Volume III, page 164) reaction of oxidation of aldehydes. It is initiated by the cations of

transition metals of higher valency:



The relative reactivities of a number of substituted benzaldehydes in this reaction are as follows (the aliphatic aldehydes are oxidized at a slightly faster rate than benzaldehyde):

p-$CH_3O-C_6H_4CHO$	3.7	C_6H_5CHO	1
p-$CH_3-C_6H_4CHO$	2.29	*p*-$Cl-C_6H_4CHO$	0.54
m-$CH_3-C_6H_4CHO$	1.61	*p*-$N\equiv C-C_6H_4CHO$	0.47

Thus, electron-donating groups speed up the oxidation reaction. In the aliphatic series, this corresponds to the higher stability of hydrocarbon free radicals which carry a larger number of electron-donating alkyls, i.e., to the sequence

$$(CH_3)_3C\cdot > (CH_3)_2CH\cdot > CH_3-CH_2\cdot$$

and, hence, to the more facile elimination of hydrogen from the carbon-hydrogen bond with the formation of a radical on the left side of the series. Therefore, saturated hydrocarbons with a normal chain when subjected to oxidation with oxygen form a mixture of

---

* The last reaction occurs rapidly and is accelerated by benzoic acid, so that under ordinary conditions the perbenzoic acid formed is consumed completely. The acid can be fixed if the reaction is conducted in a solution of acetic anhydride which acetylates perbenzoic acid into a more stable mixed peroxide, $C_6H_5C(=O)-O-O-C(=O)-CH_3$, this being accumulated.

secondary alcohols:

$$CH_3(CH_2)_nCH_2CH_3 + Co^{3+} \longrightarrow CH_3(CH_2)_n\dot{C}HCH_3 + Co^{2+} + H^+ \quad \text{(chain initiation)}$$

$$CH_3(CH_2)_n\dot{C}HCH_3 + O_2 \longrightarrow CH_3(CH_2)_nCHCH_3 \quad (O-O\cdot)$$

$$CH_3(CH_2)_nCHCH_3 + CH_3(CH_2)_nCH_2CH_3 \longrightarrow \quad (O-O\cdot)$$

$$\longrightarrow [CH_3(CH_2)_nCHCH_3 + CH_3(CH_2)_n\dot{C}HCH_3 \quad (OOH)$$

(chain propagation; 1st route)

$$CH_3(CH_2)_nCHCH_3 + Co^{2+} \longrightarrow \quad (OOH)$$

$$\longrightarrow CH_3(CH_2)_nCHCH_3 + OH^- + Co^{3+} \quad (O\cdot)$$

$$CH_3(CH_2)_nCHCH_3 + CH_3(CH_2)_nCH_2CH_3 \longrightarrow \quad (O\cdot)$$

$$\longrightarrow CH_3(CH_2)_nCHCH_3 + CH_3(CH_2)_n\dot{C}HCH_3 \quad (OH)$$

(chain propagation; 2nd route)

$$CH_3(CH_2)_nCHCH_3 + CH_3(CH_2)_n\dot{C}HCH_3 \longrightarrow \quad (O\cdot)$$

$$\longrightarrow \begin{matrix} CH_3(CH_2)_nCHCH_3 \\ | \\ O \\ | \\ CH_3(CH_2)_nCHCH_3 \end{matrix} \quad \text{(chain termination)}$$

If there is a branching of the skeleton with a tertiary hydrogen atom, the oxidation at this atom proceeds even more rapidly.

As we have seen, radicals of the allyl (and benzyl) type are formed especially readily. Therefore, olefins undergo autoxidation according to the scheme (In· = initiator):

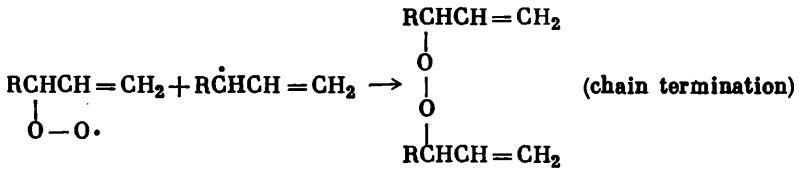
$$RCH_2CH=CH_2 + In\cdot \longrightarrow R\dot{C}HCH=CH_2 + In-H \quad \text{(chain initiation)}$$

$$R\dot{C}HCH=CH_2 + O_2 \longrightarrow RCHCH=CH_2 \quad (O-O\cdot)$$

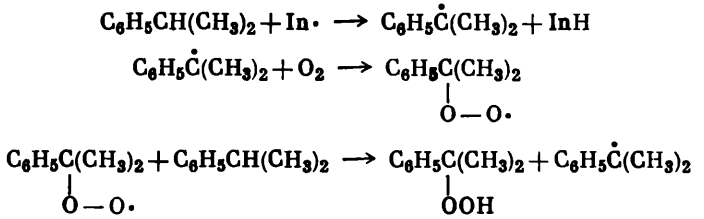
$$RCHCH=CH_2 + RCH_2CH=CH_2 \longrightarrow \quad (O-O\cdot)$$

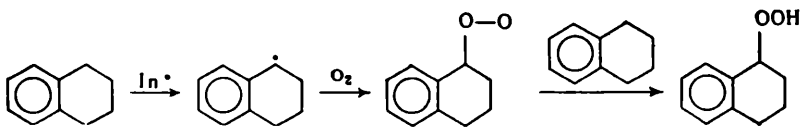
$$\longrightarrow RCHCH=CH_2 + R\dot{C}HCH=CH_2 \quad (OOH)$$

(chain propagation)

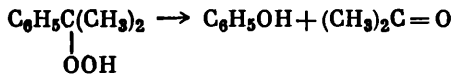


Toluene does not undergo noticeable autoxidation at room temperatures, but xylenes on standing always form a small amount of peroxides, which can be detected by the evolution of iodine from potassium iodide. As has already been pointed out, isopropylbenzene and tetralin can be completely oxidized to the hydroperoxides:

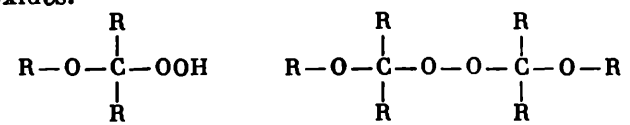




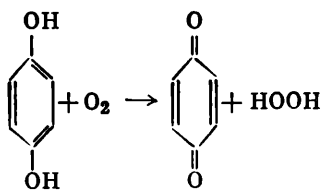
Isopropylbenzene hydroperoxide is employed in the industrial synthesis of phenol and acetone, into which it decomposes on heating:



Ethers readily undergo autoxidation, forming hydroperoxides and peroxides:



Hydroquinones in alkaline solution are oxidized by atmospheric oxygen, converting the latter into hydrogen peroxide:



This reaction is a non-chain homolytic process. Hydrogen peroxide is produced on the industrial scale by an analogous process from anthrahydroquinone. This starting material is obtained by the catalytic reduction of anthraquinone by hydrogen, so that the result of the process may be expressed by the following equation:

$$H_2 + O_2 \longrightarrow H_2O_2$$

C. Radical Addition to Double Bonds

This addition reaction occurs according to the scheme

$$X\cdot + CH_2=CH_2 \longrightarrow X-CH_2-CH_2\cdot$$
$$X-CH_2CH_2\cdot + XY \longrightarrow X-CH_2CH_2-Y+X\cdot$$

and is thus a chain reaction.

As seen from Table 15.3, both steps of the chain reaction are exothermic only for hydrogen sulphide, hydrogen bromide, hypochlorous acid, chlorine and bromine. For hydrogen chloride the second step would be endothermic. The homolytic addition of water, iodine, hydrogen fluoride and hydrogen iodide to ethylene is impossible.

TABLE 15.3. The Heats of Radical Addition Reactions (kcal/mole)

X—Y	$X\cdot + CH_2=CH_2 \uparrow$ / $\uparrow XCH_2CH_2\cdot$	$XCH_2CH_2\cdot + XY \uparrow$ / $\uparrow XCH_2CH_2Y + X\cdot$	X—Y	$X\cdot + CH_2=CH_2 \uparrow$ / $\uparrow XCH_2CH_2\cdot$	$XCH_2CH_2\cdot + XY \uparrow$ / $\uparrow XCH_2CH_2Y + X\cdot$
H—H	−40	+6	HO—Cl	−32	−17
HS—H	−16	−8	Cl—Cl	−19	−19
Cl—H	−19	+5	Br—Br	−5	−17
Br—H	−5	−11	I—I	+9	−13
I—H	+9	−27	H—OH	—	+37
H—F	—	+37			

The most thoroughly studied reaction is the radical addition of hydrogen bromide discovered by Kharasch in 1932. This reaction is initiated by traces of a peroxide and is inhibited by antioxidants, such as hydroquinone. The first observation was made on allyl bromide, which after being carefully purified from peroxides or in the presence of an antioxidant added HBr by a "normal" heterolytic mechanism in accordance with Markovnikov's rule

$$CH_2=CH-CH_2Br + HBr \longrightarrow CH_3-CHBr-CH_2Br$$

and when benzoyl peroxide or ascaridole (page 310) was added, the reaction proceeded by a chain free-radical mechanism:

$$CH_2=CH-CH_2Br+Br\cdot \longrightarrow BrCH_2-\dot{C}H-CH_2Br$$

$$BrCH_2-\dot{C}H-CH_2Br+HBr \longrightarrow BrCH_2-CH_2-CH_2Br+Br\cdot, \text{ etc.}$$

in contrary to Markovnikov's rule (the so-called **peroxide effect**). The point of attack on the olefinic carbon atom by the bromine atom is evidently determined by the lower energy content* of the generated free radical with a secondary free-radical carbon, $BrCH_2\dot{C}HCH_2Br$, as compared with the isomeric $\cdot CH_2CHBrCH_2Br$.

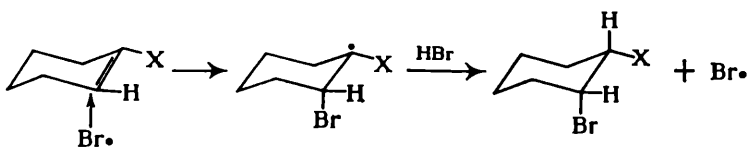
The situation is analogous with propylene (and its homologues)

$$CH_2=CH-CH_3+Br\cdot \longrightarrow BrCH_2-\dot{C}H-CH_3$$

$$BrCH_2-\dot{C}H-CH_3+HBr \longrightarrow BrCH_2-CH_2-CH_3+Br\cdot$$

while the heterolytic addition gives $CH_3CHBrCH_3$.

Interesting data have been obtained on the radical addition of HBr to 1-halogeno-1-cyclohexene: it occurs stereospecifically with the formation of *cis*-dihalogeno derivative, which is unusual for free-radical processes. In this case, this is the result of the greater possibility of attack in the axial than in the equatorial direction (see Volume II, pages 189 and 210):



It means that the second step of the chain reaction takes place so rapidly that the given chair conformation cannot flip to another conformer.

Hydrogen chloride, for the addition of which the total energy balance is favourable and only the second step is endothermic (see Table 15.3), can in principle be added by a free-radical process. But its addition to ethylene is initiated not by acyl peroxides but only by ultraviolet light or by the decomposition of *tert*-butyl peroxide at 140°C. Hydrogen chloride can be added in contrary to Markovnikov's rule to *tert*-butylethylene, the reaction being initiated by benzoyl peroxide. A primary halide, 2,2-dimethyl-4-chlorobutane, is formed to the extent of 24 per cent. The addition of hydrogen chloride to olefins by a free-radical route proceeds by short chains and is accompanied by side reactions, say, by telomerization (page 217).

* For the relation between the free energy of the transition state and the reaction rate, see Volume I, page 120.

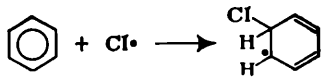
In the gas phase or in an inert solvent on illumination there can be carried out the chain reactions of chlorination and bromination of olefins and acetylene

$$Cl\cdot + CH_2{=}CHR \longrightarrow ClCH_2{-}\dot{C}HR$$

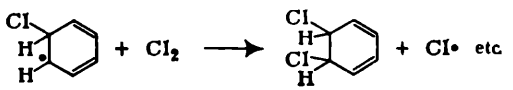
$$ClCH_2{-}\dot{C}HR + Cl_2 \longrightarrow ClCH_2{-}CHClR + Cl\cdot$$

that is there can be obtained the same final result as in an ordinary electrophilic addition of halogen. Iodine can be added to olefins on illumination only at a temperature of —55°C. All these radical reactions, however, proceed with a low quantum yield (especially with iodine) and are strongly inhibited by oxygen.

As was pointed out in Volume III (page 14), benzene is chlorinated in the light to yield a mixture of stereoisomeric hexachlorocyclohexanes. This reaction, as shown by the kinetics, proceeds by a chain mechanism with the probable first stage

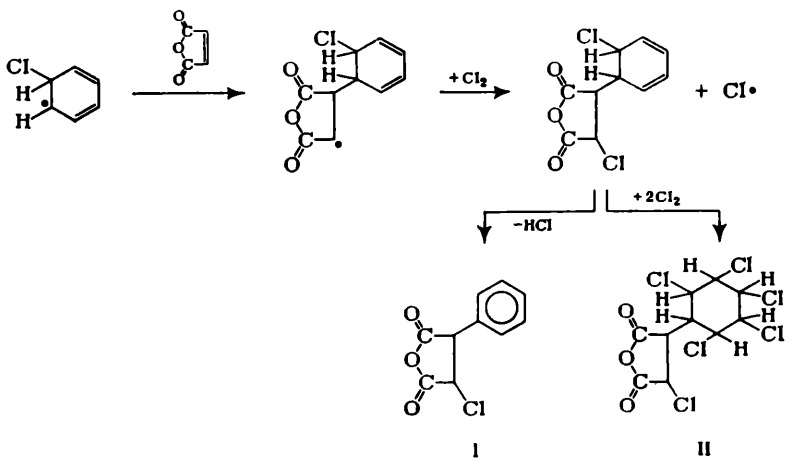


followed by



The first step can be fixed by adding maleic anhydride to the reaction mixture (a solution in CCl_4).

The reaction develops as follows:



I II

The reaction products are found to contain products I and II.

Mercaptans under the influence of acids add on to olefins by a heterolytic mechanism in accordance with Markovnikov's rule:

$$RCH=CH_2+H^+ \longrightarrow R\overset{+}{C}H-CH_3$$

$$R\overset{+}{C}H-CH_3+R'SH \longrightarrow \underset{\displaystyle SR'}{\underset{|}{RCH}}-CH_3+H^+$$

In the presence of radical chain-reaction initiators (In· = initiator) an anti-Markovnikov addition takes place (Kharasch):

$$R'SH+In\cdot \longrightarrow R'S\cdot+InH \quad \text{(chain initiation)}$$

$$\left.\begin{aligned} R'S\cdot+RCH=CH_2 &\longrightarrow R\dot{C}HCH_2SR' \\ R\dot{C}HCH_2SR'+R'SH &\longrightarrow RCH_2CH_2SR'+R'S\cdot \end{aligned}\right\} \text{(chain propagation)}$$

$$R'S\cdot+R'S\cdot \longrightarrow R'-S-S-R' \quad \text{(chain termination)}$$

Thiolic acids $RC\overset{O}{\underset{SH}{<}}$ behave in an analogous manner.

Kharasch found that in the presence of initiators—acyl peroxides—olefins add CCl_4, CCl_3Br. Later it was established that many other polyhalogenoalkanes (CCl_3I, CF_3I, CCl_2Br_2, CF_2Br_2, $CF_2BrCFClBr$, $CHCl_3$, $CHBr_3$, CHI_3, CBr_4) and certain polyhalogeno derivatives, such as CCl_3CN, CCl_3—COCl, also add on to unsaturated compounds as a result of radical chain reactions.

This may be illustrated by the following examples:

$$CCl_4+H\cdot \longrightarrow CCl_3\cdot+HCl$$

$$CCl_3\cdot+CH_2=CHR \longrightarrow CCl_3CH_2-\dot{C}HR$$

$$CCl_3CH_2\dot{C}HR+CCl_4 \longrightarrow \underset{\displaystyle CCl_3}{\underset{|}{CH_2}}-\underset{\displaystyle Cl}{\underset{|}{CHR}}+CCl_3\cdot$$

In such reactions the initiator invariably splits off the halogen atom from the polyhalogenomethyl group. Iodine is detached more easily than bromine and the latter more readily than chlorine. From $CHCl_3$ the hydrogen atom is detached more readily.

These reactions, especially for ethylene, are accompanied by polymerization which often becomes the prevailing process (see below, telomerization reactions).

In the presence of acyl peroxides (or upon illumination) aldehydes are able to add on to double carbon-carbon bonds with the formation of ketones. This reaction is also accompanied by a telomerization

reaction which may become predominant:

$$R-\overset{\overset{O}{\|}}{C}-H+In\cdot \longrightarrow R-\overset{\overset{O}{\|}}{C}\cdot+InH$$

$$R-\overset{\overset{O}{\|}}{C}\cdot+CH_2=CHR' \longrightarrow R-\overset{\overset{O}{\|}}{C}-CH_2-\dot{C}HR'$$

$$R-\overset{\overset{O}{\|}}{C}-CH_2\dot{C}HR'+R-\overset{\overset{O}{\|}}{C}-H \longrightarrow R-\overset{\overset{O}{\|}}{C}-CH_2CH_2R'+R-\overset{\overset{O}{\|}}{C}\cdot, \text{ etc.}$$

Carboxylic acids with an α-methylene group add on to olefins in the presence of peroxides or other initiators by the following reactions:

$$R-CH_2-\overset{\overset{O}{\|}}{C}-OH+In\cdot \longrightarrow R-\dot{C}H-\overset{\overset{O}{\|}}{C}-OH+InH$$

$$R-\dot{C}H-\overset{\overset{O}{\|}}{C}-OH+CH_2=CHR' \longrightarrow R-\underset{\displaystyle CH_2-\dot{C}H-R'}{\underset{|}{CH}}-\overset{\overset{O}{\|}}{C}-OH$$

$$R-\underset{\displaystyle CH_2-\dot{C}H-R'}{\underset{|}{CH}}-\overset{\overset{O}{\|}}{C}-OH+R-CH_2-\overset{\overset{O}{\|}}{C}-OH \longrightarrow R-\underset{\displaystyle CH_2-CH_2-R'}{\underset{|}{CH}}-\overset{\overset{O}{\|}}{C}-OH+R-\dot{C}H-\overset{\overset{O}{\|}}{C}-OH$$

But in this interaction there predominates a telomerization reaction.

15.5. The Telomerization (Oligomerization) Reactions

The kinetics of telomerization reactions will be discussed in Sec. 15.6.

Partial telomerization reactions have been mentioned in Volume I (page 242). An idea of these reactions can be gained from the following schemes:

I. $CCl_4+In\cdot \longrightarrow CCl_3\cdot+InCl$ (chain initiation)

$$\left.\begin{array}{l} CCl_3\cdot+CH_2=CH_2 \longrightarrow CCl_3-CH_2CH_2\cdot \\ CCl_3CH_2CH_2\cdot+CH_2=CH_2 \longrightarrow CCl_3CH_2CH_2CH_2CH_2\cdot \\ CCl_3CH_2CH_2CH_2CH_2\cdot+CH_2=CH_2 \longrightarrow \\ \qquad \longrightarrow CCl_3CH_2CH_2CH_2CH_2CH_2CH_2\cdot \end{array}\right\} \text{(chain propagation)}$$

$$CCl_3CH_2CH_2CH_2CH_2CH_2CH_2\cdot+CCl_4 \longrightarrow$$
$$\longrightarrow CCl_3CH_2CH_2CH_2CH_2CH_2CH_2Cl+CCl_3\cdot \quad \text{(chain transfer)}$$

$$CCl_3\cdot + CCl_3CH_2CH_2\cdot \longrightarrow CCl_3CH_2CH_2CCl_3 \quad \text{(chain termination)}$$

II. $$CHCl_3 + In\cdot \longrightarrow CCl_3\cdot + InH$$

$$CCl_3\cdot + CH_2=CH_2 \longrightarrow CCl_3CH_2CH_2\cdot$$

$$CCl_3CH_2CH_2\cdot + CH_2=CH_2 \longrightarrow CCl_3CH_2CH_2CH_2CH_2\cdot$$

$$CCl_3CH_2CH_2CH_2CH_2\cdot + CHCl_3 \longrightarrow CCl_3CH_2CH_2CH_2CH_3 + CCl_3\cdot$$

III. $$CH_3-\underset{\underset{O}{\|}}{C}-OH + In\cdot \longrightarrow \dot{C}H_2-\underset{\underset{O}{\|}}{C}-OH + InH$$

$$\dot{C}H_2-\underset{\underset{O}{\|}}{C}-OH + CH_2=CH_2 \longrightarrow HO-\underset{\underset{O}{\|}}{C}-CH_2CH_2\dot{C}H_2$$

$$HO-\underset{\underset{O}{\|}}{C}-CH_2CH_2\dot{C}H_2 + CH_2=CH_2 \longrightarrow HO-\underset{\underset{O}{\|}}{C}-CH_2CH_2CH_2CH_2\dot{C}H_2$$

At this stage, as has been found by R. Kh. Freidlina and A. P. Terentiev, there takes place the isomerization of the radical:

$$HO-\underset{\underset{O}{\|}}{C}\begin{matrix}\diagup\ CH_2-CH_2\ \diagdown\\ \diagdown\ \dot{C}H_2-CH_2\ \diagup\end{matrix}CH_2 \longrightarrow HO-\underset{\underset{O}{\|}}{C}-\dot{C}H-CH_2-CH_2-CH_2-CH_3$$

and further a new radical begins to grow:

$$HO-\underset{\underset{O}{\|}}{C}-\dot{C}HCH_2CH_2CH_2CH_3 + CH_2=CH_2 \longrightarrow HO-\underset{\underset{O}{\|}}{C}-\underset{\underset{CH_2-CH_2\cdot}{|}}{CH}-CH_2CH_2CH_2CH_3 \text{ etc.}$$

$$HO-\underset{\underset{O}{\|}}{C}-\underset{\underset{CH_2CH_2CH_2CH_2\cdot}{|}}{CHCH_2CH_2CH_2CH_3} + CH_3-\underset{\underset{O}{\|}}{C}-OH \longrightarrow$$

$$\longrightarrow HO-\underset{\underset{O}{\|}}{C}-\underset{\underset{CH_2CH_2CH_2CH_3}{|}}{CHCH_2CH_2CH_2CH_3} + \dot{C}H_2-\underset{\underset{O}{\|}}{C}-OH$$

Of course, each of these reactions yields a mixture of telomer-homologues (oligomers) of the general structure; for example:

$$CCl_3(CH_2CH_2)_nCl, \quad CCl_3(CH_2CH_2)_nH, \quad HOC-\underset{\underset{O}{\|}}{C}\underset{\underset{(CH_2CH_2)_nH}{|}}{HCH_2CH_2CH_2CH_3}$$

The ratio of oligomers with different n depends both on the conditions of the experiment (pressure, excess of an olefin, temperature) and on the ratio of the kinetic constants characteristic of the steps of a chain reaction.

15.6. The Kinetics of Chain Reactions

Any free-radical chain reaction involves the following characteristic part-processes: initiation, propagation, branching and termination of the chain. For example, in the photochemical chlorination of an aliphatic hydrocarbon there may be differentiated the following elementary steps, the interplay of which constitutes the mechanism of the reaction:

$$Cl_2 \xrightarrow{h\nu} 2Cl\bullet \quad \text{(chain initiation)}$$

$$\left.\begin{aligned} RH + Cl\bullet &\longrightarrow HCl + R\bullet \\ R\bullet + Cl_2 &\longrightarrow RCl + Cl\bullet \end{aligned}\right\} \quad \text{(chain propagation)}$$

$$2R\bullet \longrightarrow \text{Inactive products} \quad \text{(chain termination)}$$

Initiation of Chains. This step of a chain reaction in a system containing only valently saturated compounds gives rise to free radicals. The formation of radicals may be the result of the effect of physical factors (temperature, light, X- and γ-rays) on the reactants or compounds deliberately introduced into the reaction mixture. Free radicals can be produced by addition to the system of small amounts of special agents, **initiators**, which are capable of readily breaking down with the formation of active radicals. Examples of such initiators are: alkyl peroxides (RO—OR), acyl peroxides (RC(=O)—O—O—C(=O)R), aliphatic azo compounds (e.g., RCH(X)—N=N—CH(X)R, where X = CN, COOH, COOR'), and some organometallic compounds (R_4Pb).

Propagation of the Kinetic Chain. The propagation steps of a chain reaction involve the conversion of reactants to products with no net consumption of atoms or radicals. All the elementary reactions constituting the chain propagation step proceed with retention of a free valency. An atom or a free radical consumed in the first act of chain propagation must be regenerated in the final act of this step. Such a sequence of elementary chain propagation reactions is called a **reaction chain.** It is the multiple repetition of these reaction chains that makes a chain reaction. The **chain length** is defined as the average number of complete chains per free radical formed at the initiation step and participating in chain initiation.

The high reactivity of radicals capable of interacting with the various organic compounds by a substitution or addition reaction mechanism, say, according to the scheme

$$R\bullet + CH_2{=}CHX \longrightarrow RCH_2\dot{C}HX$$

and also of undergoing isomerization

$$CCl_3-\dot{C}H-CH_2X \longrightarrow \dot{C}Cl_2-CHCl-CH_2X$$

or decomposition

$$C_6H_5COO\cdot \longrightarrow C_6H_5\cdot + CO_2$$

is responsible for the vast variety of modes of chain propagation in the various chain reactions.

For the overwhelming majority of radical chain reactions of organic compounds the mechanism of chain propagation is characterized by the fact that in any elementary act there is formed only one new free radical (or atom) per one free radical (or atom) consumed.

There exists, however, a special class of chain reactions involving elementary acts in which there are produced two or more radicals per one consumed particle with an unpaired electron. An example is the oxidation of hydrogen by oxygen, involving the step:

$$H\cdot + O_2 \longrightarrow HO\cdot + \cdot O\cdot$$

Such elementary reactions involving the production of two or more chain centres, each of which is capable of propagating a reaction chain, are called **chain branching reactions.** Combustion and explosion proceed as branched chain reactions. Their nature and the specificity of their kinetics have been elucidated by N. N. Semenov and his school.

In the succeeding discussion we shall deal only with unbranched chain reactions.

Chain Termination. The chain-terminating step involves the destruction of free radicals, i.e., their conversion into stable molecules or the formation of only slightly active radicals (like semiquinones) incapable of propagating the chain. Chain termination accounts for the fact that the chain length in chain reactions is not infinitely great.

In radical chain reactions taking place in the liquid phase, chain termination is caused by the interaction of two radicals (**quadratic termination**). There are two modes of quadratic termination: the union of two radicals, or **recombination,**

$$C_2H_5\cdot + C_2H_5\cdot \longrightarrow C_4H_{10}$$

or their **disproportionation** with the formation of one saturated and one unsaturated molecule:

$$C_2H_5\cdot + C_2H_5\cdot \longrightarrow CH_2=CH_2 + CH_3-CH_3$$

The low concentration of radicals in the liquid phase makes the termination of the reaction chain by way of either recombination or disproportionation very nearly improbable. It is this factor that enables the interaction of the radical with the surrounding molecules

to be repeated many times until the radical is destroyed as the result of chain termination.

The reaction chain length is determined by the ratio of the rates of propagation and termination steps.

In a number of cases the chain termination step gives rise to by-products. The ratio of the yields of main products (obtained at chain propagation steps) and by-products depends on the chain length. The chain length in its turn is dependent on the conditions of the reaction and may vary in the course of the reaction, for which reason ordinary radical chain reactions cannot be described by a single stoichiometric equation. Only in those cases when chain reactions have a large chain length can they be formally described by one stoichiometric equation.

The concentrations of reacting compounds and the rate of their consumption can be determined experimentally for any radical chain reaction; the concentration of transiently formed free radicals is difficult to measure. In spite of this, kinetic equations for any elementary step contain quantities denoting radical concentrations. For instance, for a reaction whose reaction chain consists of only two elementary acts

$$AB + C\cdot \xrightarrow{k_1} AC + B\cdot \tag{1}$$

$$CD + B\cdot \xrightarrow{k_2} BD + C\cdot \tag{2}$$

the rate of consumption of the reactants AB and CD and the rate of formation of the reaction products AC and BD are given by the equations (3) and (4) which contain radical concentrations:

$$-\frac{d[AB]}{dt} = \frac{d[AC]}{dt} = k_1 [C\cdot][AB] \tag{3}$$

$$-\frac{d[CD]}{dt} = \frac{d[BD]}{dt} = k_2 [B\cdot][CD] \tag{4}$$

In order to eliminate radical concentrations from the equations, a rather fruitful assumption of the **quasi-stationary state** of the system is introduced.

A chain reaction involves an initial step with the concentration of radicals increasing from zero to the "average" value; this is called the **non-steady state** or **non-stationary state** condition. With increasing concentration of radicals the rate of their destruction increases. When the rates of creation of radicals and of their destruction become closer to each other, the quasi-stationary phase of the reaction sets in; in this phase the concentration of radicals may be considered to be constant.

When the reaction is nearing to an end and the source of formation of new radicals is exhausted, their concentration rapidly falls to

zero and the reaction again assumes a non-steady state character. If the time length of the non-steady phases of the reaction is considerably shorter than that of the step with a constant concentration of radicals, the quasi-steady-state method is applicable to this reaction.

Using the quasi-steady-state method and making certain other simplifications, say, introducing the assumptions that chain termination takes place either by the combination or by the disproportionation of radicals, or that radicals of the same species are predominantly consumed in termination reactions (for example, radicals C· in scheme 3, and radicals B· in scheme 4), it has been possible to derive a number of kinetic equations which are in good agreement with the experimental results.

The most thoroughly elaborated methods are those of investigation into the kinetics of radical chain polymerization of vinyl monomers of the structure:

$$CH_2=CHX \qquad \text{and} \qquad CH_2=CXY$$

This is accounted for by the importance of such processes and also by the fact that many of these reactions have a large kinetic chain length, proceed practically without formation of side products, and in the case of homopolymerization the reacting system contains only one monomer.

The dependence of the rate of polymerization on the concentration of monomer is often found to be complicated. For instance, it has been found for styrene that when the degree of conversion is about 60 per cent in the initiated bulk polymerization the reaction is first-order with respect to the monomer concentration, and in dilute solutions the same reaction is second-order. According to the later findings of Mayo the reaction order of the polymerization of styrene in solution is close to 2.5. In the case of polymerization of vinyl acetate the apparent reaction order also depends on the range of monomer concentrations under study.

The mechanism of polymerization may be expressed by the following scheme in which R· denotes the radical formed at the stage of initiation of the kinetic chain, M is the monomer molecule, R_n is the polymer molecule containing n monomeric units, and M· is the radical resulting from the detachment of any atom from the monomer molecule.

(1) *Initiation*:

$$\text{Initiator} \longrightarrow 2R\cdot \qquad \text{(rate of formation of R}\cdot = J)$$

$$R\cdot + M \longrightarrow RM\cdot \qquad \text{(rate constant } k_p)$$

(2) *Propagation of the kinetic chain*:

$$RM\cdot + nM \xrightarrow[\text{(growth of radical)}]{} R(M)_nM\cdot \qquad \text{(rate constant } k_p)$$

$$R(M)_nM\cdot + M \xrightarrow[\text{(chain transfer)}]{} RM_{n+1} + M\cdot \qquad \text{(rate constant } k_f)$$

(3) *Termination of the kinetic chain*:

$$2R(M)_nM\cdot \longrightarrow R_{2n+2} \quad \text{(rate constant } k_t\text{)}$$

$$2R(M)_nM\cdot \longrightarrow 2R_{n+1} \quad \text{(rate constant } k_t'\text{)}$$

This scheme has been worked out with the following simplifying assumptions introduced. It is assumed that the radical growth rate constant (k_p) is independent of the chain length of the radicals, and the rate constants for chain transfer (k_f) and for chain termination (k_t and k_t') are also independent of the radical chain length and, besides, are constant at a given temperature. It is also assumed that the chain termination is quadratic and the chain length is great. So, with a good degree of approximation we can obtain the following equation for the rate of monomer consumption:

$$-\frac{d[M]}{dt} = \sum_n k_p [\cdot R_n][M] \tag{5}$$

In order to eliminate the quantity corresponding to the radical concentrations, $[\cdot R_n]$, from this equation, it is assumed that the system is in the quasi-stationary state, in which case Eq. (5) may be transformed into the following equation:

$$-\frac{d[M]}{dt} = k_p [M] \left(\frac{J}{k_t + k_t'}\right)^{1/2} \tag{6}$$

which no longer contains the radical concentration.

An important corollary of Eq. (6) is the proportionality between the rate of polymerization and the square root of the rate of initiation. This equation reflects the characteristic properties of radical chain reactions, namely the possibility of increasing the rate of a chain reaction by increasing the rate of initiation (for example, by addition of small amounts of initiators) and the possibility of diminishing the rate of the reaction by enhancing the rate of chain termination, i.e., by increasing the sum of $k_t + k_t'$ (e.g., with the aid of added inhibitors).

The conclusion as to the proportionality of the rate of a chain reaction to the square root of the rate of initiation is applicable not only to polymerization reactions but is of general importance for chain reactions with a large chain length and quadratic termination, which satisfy the principle of the quasi-stationary state.

Using Eq. (6), one can easily derive certain other relationships between the rate constants of the elementary steps of the process. Thus, for example, for polymerization reactions the mean kinetic chain length x can be written down, by definition, as follows:

$$x = -\frac{d[M]}{dt} \Big/ J \tag{7}$$

Introducing the value of $-\frac{d[M]}{dt}$ into expression (7) from Eq. (6), we obtain:

$$x = k_p [M] \frac{J^{-1/2}}{(k_t + k_t')^{1/2}} \tag{8}$$

A. Determination of Chain-Transfer Constants in Radical Telomerization Reactions

As has already been said, by radical telomerization is meant the chain reaction of a vinyl monomer with any chain-terminating compound called the telogen (CCl_4, CH_3CHO, CH_3COOH in the above examples), which results in the formation of low-molecular-weight products known as telomers. Their molecules are built by the union of molecules of an unsaturated compound, the terminal groups being the fragments of telogen molecules. In a general form, this reaction may be formulated as follows:

$$A-B+nCH_2=CXY \longrightarrow A-(CH_2-CHXY)_n-B$$

where AB is any compound capable of adding on to an unsaturated compound, and $n = 1, 2, 3$, etc.

Designating the monomer molecule by M, as before, we can describe the mechanism of telomerization reaction by the following scheme:

(1) *Initiation*:

$$\text{Initiator} \longrightarrow 2R\cdot$$
$$R\cdot + A-B \longrightarrow R-B+A\cdot$$
$$A\cdot + M \longrightarrow A-M\cdot$$

(2) *Propagation*:

$$A-M_n\cdot + A-B \xrightarrow{k_f} A-M_n-B+A\cdot \quad \text{(chain transfer)}$$
$$A-\dot{M}_n + M \xrightarrow{k_p} A-M_{n+1}\cdot \quad \text{(radical growth)}$$

(3) *Termination*:

$$2R\cdot \longrightarrow \text{Inactive products}$$

where R· is any radical formed in the system.

The overall kinetics of such reactions is evidently extremely complicated.

A number of simplifying assumptions should also be made in deriving kinetic equations for telomerization reactions, namely the quasi-stationary state method, quadratic chain termination, a large kinetic chain length, etc. Some of the simplifying assumptions used in the derivation of kinetic equations for polymerization reactions

are however inapplicable here, say, a large length of the molecular chain and the independence of the rate constants of elementary reactions on the radical chain length. Besides, it is necessary that account be taken of the fact that, in contrast to polymerization reactions, the rate of the chain-transfer reaction has an effect on the overall rate of telomerization.

The study of the kinetics of the chain propagation step consisting of two competing reactions, chain transfer and radical growth, has proved to be fruitful for telomerization reactions. It is this stage that involves the consumption of the monomer and telogen and the formation of the main products (telomers). With a sufficient kinetic chain length the initiation and termination steps affect little the distribution of the yields of telomers. Therefore the ratio of the molar fraction of the telomer containing n monomeric units ($A-M_n-B$) to the total molar fraction of the other telomers containing more than n monomeric units ($\sum_{n+1}^{\infty} A-M_i-B$) is determined by the competition between the two elementary reactions indicated. Hence, we obtain an equation for calculating the ratio of the rate constant for chain transfer, k_f, to that for propagation, k_p (this ratio is called the **transfer constant** and is denoted by $C_n = k_f/k_p$):

$$\frac{d[A-M_n-B]}{d[A-M_i-B]} = \frac{k_f n [A-M_n\cdot][AB]}{k_p n [A-M_n\cdot][M]} = \frac{k_f}{k_p}\cdot\frac{[AB]}{[M]} = C_n\frac{[AB]}{[M]} \qquad (9)$$

The molar yield of a telogen with a number of monomeric units n and also the sum of the molar yields of all the telogens with a number of monomeric units larger than n can be easily determined experimentally just as the concentrations of the reactants.

A number of other equations have been proposed for determination of transfer constants.

For a number of systems, such as, for example, the telomerization of olefins by carbon tetrachloride or chloroform, it has been found that the quantity C_n varies considerably on passing from $n = 1$ to $n = 2$ and $n = 3$; for the higher values of n the quantity C usually becomes constant. Further in the text the constants C_1, C_2, C_3, and C_n will be called partial transfer constants.

The values of C_n for any particular reaction must not depend on the reactant concentrations; the values of C_n for different systems are governed by the nature of the telogen and monomer.

Once the values of the partial constants in a carefully controlled reaction are determined it is possible to use them for calculating the yield of any telomer in a reaction conducted under any concrete conditions. For calculations use is made of an expression in which F_n signifies the fraction of all the growing chains determining the

yield of a telomer with a number of monomeric units n:

$$F_n = C_n \frac{[AB]}{[M]} \left\{ \prod_{i=1}^{n} \left(C_i \frac{[AB]}{[M]} + 1 \right) \right\}^{-1}$$

The chain transfer constants may serve as a sufficiently simple method of estimating the relationship between the structure and reactivity of the monomer, telogen and telomeric radicals formed.

The use of the quasi-stationary state method and other simplifying assumptions has made it possible to derive a number of formulas [(6), (8), (9)] for the rate of consumption of the reactant, the mean kinetic chain length, and partial transfer constants, in which the rate constants for the elementary reactions, k_p, k_f and k_t, are always contained in the form of ratios. For the individual values of rate constants of the elementary reactions to be determined, additional data are required, for example, the steady values of radical concentrations must be measured and the rate of the reaction under non-steady state conditions must be studied.

Particularly wide use for determination of the individual rate constants of the elementary reactions of a chain process is made of the **rotating-sector method.** Photochemical reactions are carried out under conditions of intermittent illumination. Periodical interruption of illumination is achieved by using a rotating circular disc with one or more segments removed. The measurement of reaction rates under continuous and intermittent illumination conditions with a known length of dark periods enables the lifetime of the kinetic chain to be determined.

Telomerization reactions are valuable for syntheses since it allows, by way of a single procedure, to pass from the simplest olefin and telogen to oligomers (i.e., telomers) with a chain of several carbon atoms (from 2-3 to 20-30), containing one or more functional groups. A disadvantage of the telomerization reaction is the impossibility of preparing a single individual telomer and the necessity to separate the resulting mixture, in which each of the telomers constitutes a relatively small portion. This shortcoming is immaterial if each of the telomers is used up completely.

Radical polymerization reactions do not differ, in principle, from telomerization reactions, except that in preparing high-molecular-weight polymers the end groups, which are so important in telomers, are not noticeable in polymers because of the quantitative predominance of the thousand-fold repetition of the monomer fragment united into a single chain. Like telomerization, polymerization is initiated by a free radical. Usually, this is the decomposition product of a peroxide (R· or R—CO· or R—O—O·, etc.) or of the azodinitrile

$$\begin{matrix} \| \\ O \end{matrix}$$

of isobutyric acid [$(CH_3)_2\dot{C}(CN)$], or else of a diazoamino compound ($C_6H_5\cdot$ or $C_6H_5—N=N\cdot$). This free radical remains to be attached to the beginning of the polymer skeleton. As regards the end of the polymer molecule, it may be either a hydrogen abstracted from the monomer or any other atom of the same origin or even, as shown by S. S. Medvedev, the free-radical end immobilized due to the viscosity of the medium and gradually oxidized by atmospheric oxygen or undergoing any one of the chain termination reactions, say, recombination. Such "stuck-in-the-polymer" free-radical ends of macromolecules (and probably peroxides formed from them and O_2) are responsible for the polymerization of the monomer being often caused by seeding the polymer.

Chapter 16

Carbenes

In a wide range of reactions, some of which are given below, the unstable intermediates, which however are clearly identified, are the particles CH_2 and their various derivatives of the types CHR, CR_2, CRR′, where R = hydrocarbon radicals, their functional substituted compounds, the halogens, etc. Such particles with a formally divalent carbon atom are known as **carbenes** (Doering). The simplest carbene is free methylene. No carbenes have been obtained in the stable state as individual substances. Nevertheless, in chemical behaviour and physical properties the carbenes are clearly identified as reaction intermediates.

The Nature of Carbenes. It may be visualized that free methylene (and carbenes are its derivatives) exists either as a diradical $\uparrow\uparrow$ CH_2 (*sp*-hybridization, triplet optical state, the spins of both electrons on unhybridized orbitals are parallel) or is in a state in which the spins of both free electrons are paired (sp^2-hybridization, singlet state, $\uparrow\downarrow$ CH_2). The solution of this problem has taken much time and has presented formidable difficulties since the concentrations of carbene in a gas or solution are low, and the theoretical calculations based on the various approximations have given conflicting results. At present, on the basis of the optical studies carried out by Herzberg and the EPR spectrum determined by Murray the diradical triplet state may be regarded as the ground state, at least for hydrocarbon carbenes. The singlet state which has a higher energy is characteristic of the carbenes obtained by photolysis.

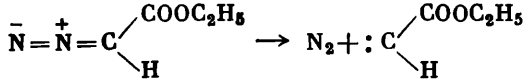
Methods of Preparation of Carbenes. 1. The commonest method of generation of methylene is the photolysis of diazomethane or ketene (Norrish):

$$CH_2=\overset{+}{N}=\overset{-}{N} \xrightarrow{h\nu} :CH_2+N_2$$

$$CH_2=C=O \xrightarrow{h\nu} :CH_2+CO$$

An analogous route is applicable for the preparation of substituted carbenes.

For example, from diazoacetic ester there is formed the corresponding carbene—**carbethoxymethylene** (I. A. Dyakonov):



2. Methylene iodide reacts with zinc to give $I-CH_2-ZnI$ which decomposes with the evolution of methylene:

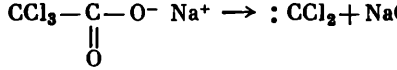
$$I-CH_2-ZnI \longrightarrow :CH_2+ZnI_2$$

3. The decomposition of organomercury compounds of the $Cl-CH_2-HgCl$ type (O. A. Reutov) and also of compounds $X-CRR'-HgX$ in general (Seyferth) under the action of agents binding HgX_2 leads to the generation of carbene CRR' (R and R' may be a radical or a halogen).

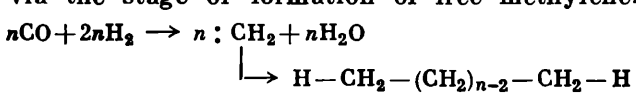
4. Halogenomethanes when reacted with strong bases form carbenes:

$$CH_2Cl_2+C_4H_9Li \longrightarrow :CHCl+C_4H_{10}+LiCl$$
$$CHCl_3+OH^- \longrightarrow :CCl_2+H_2O+Cl^-$$

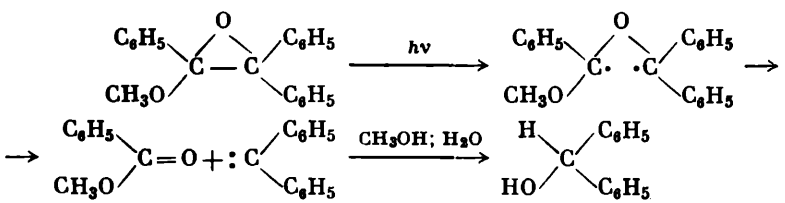
5. The pyrolysis of CCl_3COONa in an inert solvent gives dichlorocarbene (W. Wagner):



6. The preparation of synthol from carbon monoxide and hydrogen over cobalt and other catalysts (see Volume I, page 87) probably proceeds via the stage of formation of free methylene:



An interesting photodecomposition of methoxy oxides of the indicated structure in methanol with the formation and subsequent conversion of carbene has been described by T. I. Temnikova:



Reactions of Carbenes. 1. The first reaction, which proved in principle the existence of free methylene, was its action in a gaseous

current (under the conditions used by Paneth for the reaction of free methyl with lead mirror, see page 194) on tellurium or selenium mirror. This gave rise to a polymer of the tellurium or selenium analogue of formaldehyde, $(CH_2Se)_n$ and $(CH_2Te)_n$. Tin, lead and mercury were not affected by free methylene.

2. Free methylene generated by the photolysis of diazomethane adds on to carbon monoxide, forming ketene in poor yield (Staudinger, Kupfer):

$$:CH_2 + CO \longrightarrow CH_2=C=O$$

3. It has recently been proved that methylene generated by the same method adds on to nitrogen (nitrogen was labelled with the isotope) and forms diazomethane (nitrogen-labelled) in low yield:

$$:CH_2 + {}^*N_2 \longrightarrow CH_2={}^*\overset{+}{N}-\overset{-}{N}{}^*$$

4. Characteristic reactions are the additions of carbenes across the free *p*-pairs of electrons of phosphorus, nitrogen, oxygen, which leads, at least at the first stage, to the formation of ylides (see page 189) which are stable in the case of alkylidenetriarylphosphoranes and undergo further rearrangement in the case of oxygen and nitrogen:

$$(C_6H_5)_3P + :CH_2 \longrightarrow (C_6H_5)_3P=CH_2 \longleftrightarrow (C_6H_5)_3\overset{+}{P}-\overset{-}{C}H_2$$

$$\begin{matrix} & & CH_3CH_2 & & \\ & & \diagdown & & \\ & & O & :+:CH_2 & \longrightarrow \\ & & \diagup & & \\ & & CH_3CH_2 & & \end{matrix}$$

$$\longrightarrow \begin{matrix} CH_3CH_2 & & \\ \diagdown & & \\ O & -CH_2 & \longrightarrow CH_3CH_2-O-CH_2CH_2-CH_3 \\ \diagup & & \\ CH_3CH_2 & & \end{matrix}$$

$$R_3N :+: CH_2 \longrightarrow \begin{matrix} \boxed{R} & & \\ \diagdown & & \\ R-N & -CH_2 & \longrightarrow \\ \diagup & & \\ R & & \end{matrix} \begin{matrix} R & & \\ \diagdown & & \\ N & -CH_2R & \\ \diagup & & \\ R & & \end{matrix}$$

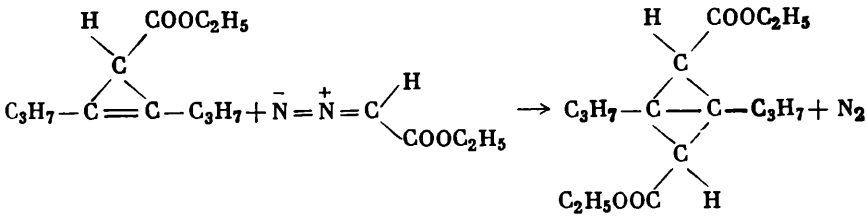
5. Carbenes add on to the double C=C bond, giving cyclopropanes:

$$\begin{matrix} & & & CH_2 & \\ \diagdown & & \diagup & & \diagdown \\ C=C & +:CH_2 & \longrightarrow & C & -C \\ \diagup & & \diagdown & & \diagup \end{matrix}$$

$$\begin{matrix} Cl & & Cl & & CCl_2 & \\ \diagdown & & \diagup & & \diagup & \diagdown \\ C=C & +:CCl_2 & \longrightarrow & Cl_2C & & -CCl_2 \\ \diagup & & \diagdown & & & \\ Cl & & Cl & & & \end{matrix}$$

By adding carbethoxymethylene to the homologues of carbethoxycyclopropene prepared by the action of the same carbene on homolo-

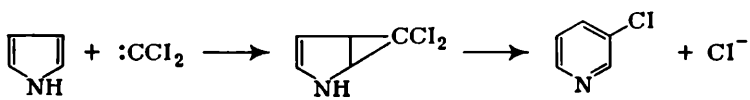
gues of acetylene (see below) I. A. Dyakonov obtained homologues of dicarbethoxybicyclo[1.1.0]butane; for example:



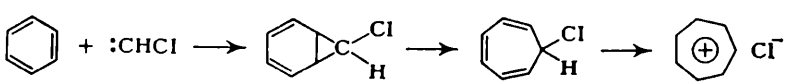
Carbenes can also add to benzene across the π-bond (Meerwein). The resulting norcaradiene then undergoes isomerization to cycloheptatriene (for this reaction, see also page 159), so that methylene, as it were, inserts itself into benzene:

A small amount of toluene is also formed along with norcaradiene.

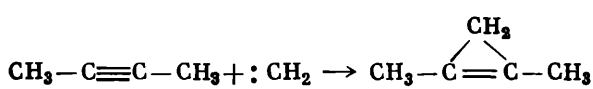
A similar procedure is used to convert pyrrole into β-chloropyridine in the presence of $:CCl_2$:



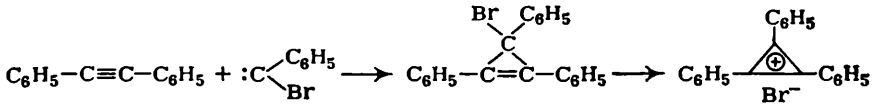
Adding chlorocarbene to benzene, D. N. Kursanov and M. E. Volpin prepared the tropylium cation (see Sec. 13.4, B):



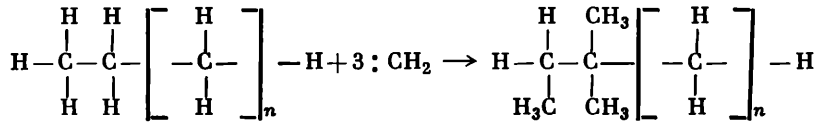
Carbenes can also be added to the triple bond. Doering synthesized dimethylcyclopropene by addition of methylene (from diazomethane) to dimethylacetylene (cyclopropene itself is not formed from acetylene):



The triphenylcyclopropenylium cation has been obtained by the addition of phenylbromocarbene to diphenylacetylene (Breslow):



6. Methylene produced by the photolysis of diazomethane reacts with saturated hydrocarbons, methylating them in a random manner; for example:



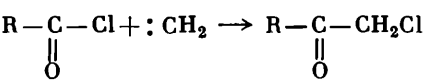
A faster and more selective reaction is shown by carbenes bearing electron-accepting substituents. According to reaction velocity and selectivity they are arranged in the following order (Doering):

$$:CH_2 < :CHCOOC_2H_5 < :C(COOC_2H_5)_2$$

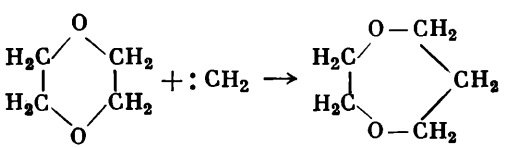
7. Carbenes react with the chlorides of some non-transition metals. One example is the conversion described by O. A. Reutov:

$$HgCl_2 + :CHCl \longrightarrow Cl_2CHHgCl$$

8. The reaction with acid chlorides proceeds in a similar way:



9. Carbenes are capable of inserting into C—O bonds (Meerwein). Such an insertion is possible for the carbon-oxygen bonds in the ring, for example:

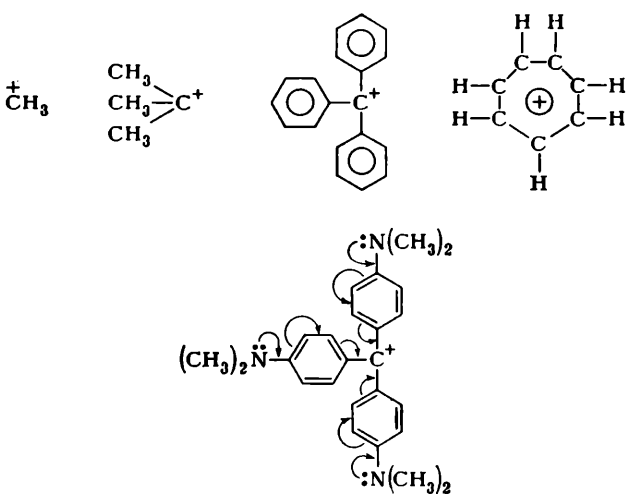


10. Carbenes of more complex structure are able to undergo rearrangements of the types described in 4 and 9 and of the types discussed in Sec. 20.2.

Chapter 17

Carbonium Ions

At various places in this course, beginning from the section devoted to the nucleophilic substitution of a halogen in alkyl halides, we have dealt with the reactions of cations bearing a positive charge on a carbon atom. **Carbonium ions** (carbon cations) are particles of various energy, and their energy content and reactivity are invariably associated with the degree of delocalization of the positive charge. Delocalization may extend to other carbon atoms or aromatic systems linked to a carbonium ion, or else to non-carbon atoms. Low-energy ions will be conditionally called here stable carbonium ions. The effect of charge delocalization may be illustrated by the following series of cations arranged in order of gradually increasing stability (the reverse of the energy content):



While the methyl cation is not detected in solutions, the existence of tertiary carbonium ions of the *tert*-butyl type can be proved in

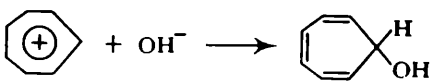
a number of cases on the basis of the kinetics of nucleophilic substitution reactions (the S_N1 mechanism), stereochemical data (racemization in nucleophilic substitution reactions), and sometimes from NMR spectra.

In tertiary carbonium ions, the positive charge on the central atom is partially cancelled by the delivery of electrons from the alkyl groups due to the inductive ($-I$) effect. In this way the charge is delocalized, i.e., is shared between the central carbon atom and the alkyl groups attached to it. Of course, the greater part of the positive charge is on the central carbon atom.

The triphenylmethyl cation, which possesses characteristic absorption frequencies in the visible region of the spectrum, can be identified from the absorption spectra. Thus, triphenylchloromethane in solution in liquid SO_2 is dissociated into a solvated yellow-coloured carbonium ion and an anion. The dissociation of triphenylchloromethane also takes place in solution in antimony pentachloride (the $SbCl_6^-$ anion), in stannic chloride and in sulphuric acid.

The considerably greater stability of the triarylcarbonium ion is due to its central positive charge being delocalized over the three aromatic nuclei—over six *ortho*- and three *para*-carbon atoms (a total of ten carbon atoms). The greater charge is nevertheless borne by the central carbon atom since the conjugation (resonance) and delocalization are interfered with by the propeller-shaped structure of the triphenylmethyl cation which is not quite planar because of steric hindrances.

An ideal delocalization of the positive charge over the seven carbon atoms of the planar tropylium ion (see Chapter 13) renders this cation quite stable even in aqueous and alcoholic medium, though it is capable of reacting with more powerful nucleophiles than water and alcohol, adding them to any of its seven carbon atoms:



And, finally in the cation of the dye crystal violet the point of primary importance is the delocalization of the charge of the carbonium centre not so much over the nine *ortho*- and *para*-carbon atoms of the phenyl groups as over the three dimethylamino groups, each of which becomes nearly one-third ammonium, and these three groups receive the major part of the cationic charge.

Thus, the cation of triphenylmethane dyes may be called a carbonium ion only with strong reservations. Recombination reactions of this cation with the anions of very weak acids, say, with OH^-, however, take place at the nearly chargeless methyl carbon atom.

It is for this reason that they proceed slowly, with a considerable activation energy, and may be regarded as reactions with transfer of the reaction centre: instead of N^+, the methyl carbon is attacked, which is quite understandable since nitrogen cannot add a fifth substituent.

Since the carbonium carbon in carbonium ions is in a state of sp^2-hybridization (just as in olefins), the carbonium ion must have a planar trigonal structure. There is an additional factor, which reduces the energy of the carbonium ion and contributes to its formation, when the molecule is sufficiently branched and is subject to steric hindrances. The role of this factor has already been discussed (see Volume III, page 263). It boils down to the fact that steric interaction (repulsion of the non-bonded groups) in the tetrahedral molecule is stronger than in the planar cation since on conversion to the cation the valence angles increase from about 109 to about 120°. Along with electrostatic interactions, this is one more factor responsible for the more facile formation of a cation, say, from *tert*-butyl chloride, as compared with the formation of a cation from *sec*-propyl chloride. The steric factor begins to play an even more crucial part in strongly branched molecules.

As was stated in Volume I (page 105), in the case of compounds capable, under certain conditions, of dissociation with the formation of a carbonium ion, substitution reactions at a saturated carbon atom may proceed by the S_N1 mechanism. Reactions that take place by this mechanism are two-stage processes and consist of the slow reversible formation of a carbonium ion and the fast reaction of the ion with a nucleophile:

$$\text{—C—X} \underset{k_2(2)}{\overset{k_1(1)}{\rightleftharpoons}} \text{—C}^+ + \text{X}^-$$

$$\text{—C}^+ + \text{Y}^- \xrightarrow{k_3(3)} \text{—C—Y}$$

The kinetics of the reaction are determined by the first, slow step. Therefore, in the limiting case, the overall rate of the reaction may obey the equation:

$$v = k_1[\text{RX}]$$

This rather rare case is realized only if the rate constant k_3 by far exceeds the rate constant for the reaction which is the reverse of heterolysis (k_2). The cause is that during the course of the reaction there is gradually accumulated the X^- ion, while the concentration of the reagent Y^- introduced decreases constantly and, hence, the forward reaction (1) is increasingly retarded.

A more general expression typical of the S_N1 reaction may be written in the following form*:

$$v = k_1 [RX] \left\{ 1 + \alpha \frac{[X]}{[Y]} \right\}^{-1}$$

where $\alpha = k_2/k_3$.

At low values of α this expression becomes simplified and, as has already been said, reduces to the previous formula.

The stereochemical result of a reaction proceeding by the S_N1 mechanism is either racemization or racemization accompanied by inversion of configuration. If the cation resulting from the slow step of the reaction is sufficiently stable, it has a chance to adopt a planar configuration before being attacked by the nucleophile. In this case, there occurs racemization since for a planar cation the direction of attack (above or below its plane) is immaterial. But if the cation is attacked before the anion has been removed to a sufficient distance and, consequently, before the carbonium ion has assumed an ideal planar form, then the direction of attack becomes important and it will be accomplished predominantly from the side opposite to the leaving group. Then, there will be more elementary acts accompanied by inversion of configuration than those taking place with retention of configuration. Thus, while complete racemization is an indication of the S_N1 mechanism and, hence, of the formation of carbonium ions in solution, complete inversion of configuration points to the S_N2 mechanism. Intermediate cases cannot be interpreted in such a strict manner.

For reactions occurring by the S_N1 mechanism, just as for the majority of organic reactions, the role of the solvent is very great. The point is that the heterolysis of the C—X bond requires a high energy and this energy is supplied by the solvent. For the reaction to proceed by the S_N1 mechanism, the solvent must have electrophilic properties, i.e., must be capable of binding the halide ion being removed. These requirements are primarily satisfied by protic solvents which are able to form hydrogen bonds or to bind the leaving group by its proton. Such solvents are acids (especially, stronger acids), water to a lesser extent, and alcohols to an even lesser degree. The characteristics of a number of solvents are listed in Table 17.1.

Solvation of the cations formed is evidently also of importance, but this question is less clear. In any event, no S_N1 reactions take place without the anion being solvated. Thus, in a very polar but nucleophilic and aprotic solvent, such as dimethyl sulphoxide,

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* The expression typical for S_N2 reactions is

$$v = k_1 [RX] [Y]$$

even the reactions of *tert*-butyl halides fail to proceed by the S_N1 mechanism.

Reactions of the S_N1 type are easily accomplished by the action of silver salts under suitable conditions. The silver ion forms a stable bond with the halide ion and detaches it from the molecule more energetically than does the solvent; besides, the anion is removed from the sphere of the reaction, as a result of which the reaction, which is the reverse of the heterolysis of the alkyl halide, is slowed down (or prevented).

TABLE 17.1. **Dielectric Constants of Solvents (at 20°C)**

Protic solvents		Aprotic solvents	
solvent	dielectric constant	solvent	dielectric constant
CH_3COOH	6-6.5	$C_2H_5OC_2H_5$	4.5
C_6H_5OH	9-10	$CH_3OCH_2CH_2OCH_3$	6.5-7
$(CH_3)_3COH$	10-11	Tetrahydrofuran	7-7.5
NH_3	22 (at −33°C)	CH_3COCH_3	20-21
		$C_6H_5NO_2$	35-36
C_2H_5OH	25	CH_3CN	36-37
F_3CCH_2OH	27	CH_3NO_2	36-37
CH_3OH	32-33	$HCON(CH_3)_2$	37-38
$HOCH_2CH_2OH$	38	$(CH_3)_2SO$	45-49
HCOOH	56	$OP[N(CH_3)_2]_3$ (hexameta-pole)	30
H_2O	81		
Dioxan	2-2.5		

Reactions that proceed by the S_N2 mechanism are, on the contrary, retarded in protic solvents since such solvents, while forming hydrogen bonds with reagents, reduce their nucleophilic activity. Thus, in protic solvents the nucleophilicity of halide anions decreases in the following order:

$$I^- > Br^- > Cl^- > F^-$$

The least active of these ions is the fluoride ion, which is capable of forming stable hydrogen bonds. In aprotic solvents the difference between these nucleophiles is not so noticeable and even the order in the series may vary considerably.

Though the transitory existence of carbonium ions as intermediates formed during the course of many organic reactions has been proved by indirect means (kinetic measurements, the stereochemical behaviour in reactions, etc.), the spectra of a number of alkyl cations have been taken only recently by Olah. He observed the NMR spectra of solutions of alkyl fluorides in antimony pentafluoride.

The reaction

$$AlkF + SbF_5 \longrightarrow Alk^+ SbF_6^-$$

gives the salt of the alkyl cation, antimony pentafluoride (a strong Lewis acid and an acceptor of the fluoride ion) being in excess. For the *tert*-butyl cation the NMR spectrum shows a single peak (just as for the parent fluoride), but it is shifted to the region of weak

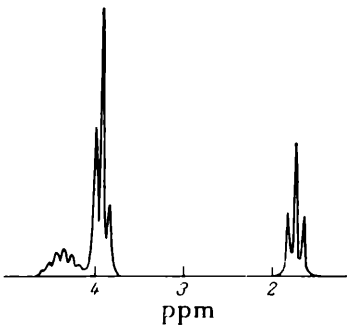


Fig. 17.1.

The NMR spectrum of the cation $(CH_3)_2\overset{+}{C}CH_2CH_3$ in a solution of SbF_5.

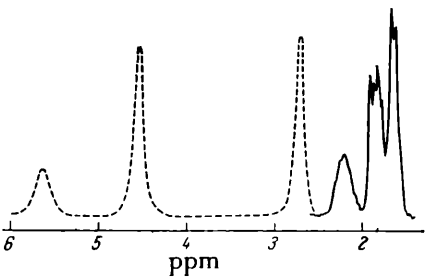


Fig. 17.2.

The NMR spectrum of adamantyl fluoride in solution in CCl_4 (heavy lines) and of the adamantyl cation formed from it by the action of SbF_5 (broken lines).

fields unusual for methyl protons (4.35 ppm on the δ scale), while the proton signal in $(CH_3)_3CF$ shows up at 1.30 ppm. Figure 17.1 shows the spectrum of the cation $(CH_3)_2\overset{+}{C}CH_2CH_3$ taken under the same conditions. On the right at about 1.75 ppm is the triplet of the methyl of the ethyl group (splitting on the protons of CH_2). The triplet at about 3.9 ppm is the proton signal of two equivalent methyl groups; the splitting is due to the interaction of the protons of these groups with those of the CH_2 group via the carbon atom that separates them. Finally, there is a slightly intensive multiplet—the signal of a methylene group (splitting on the protons of methyl groups). It should be noted that the signal of the methyl next to a positively charged carbon atom is situated at about 4 ppm, a case not observed for ordinary organic compounds. Moreover, the spin-spin splitting constant in the signal of the protons of single methyls is very high in spite of the fact that they are separated by a carbon atom from the methylene group.

It is interesting that under these conditions no cations of the type $R—CH_2^+$ (the least stable cations) have been observed.

By the action of SbF_5 on adamantyl fluoride there has been obtained the adamantyl cation

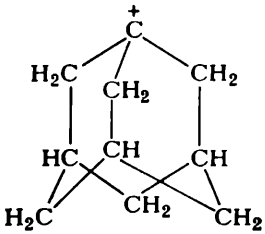
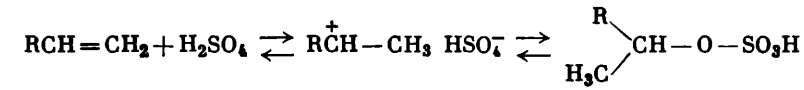


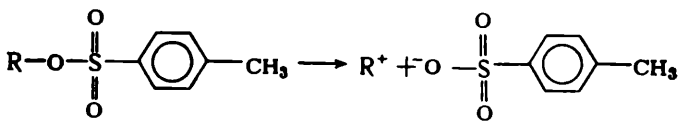
Figure 17.2 gives the NMR spectra (Volume II, page 292) of the parent adamantyl fluoride in CCl_4 and the adamantyl cation. On conversion of $C_{10}H_{15}F$ into $C_{10}H_{15}^+$ the pattern of the peaks changes sharply: under the influence of the positive charge the peaks move to the side of weak fields and break apart from each other. According to the three species of hydrogen atoms—in α-methylene groups (6 atoms), β-methine groups (3 atoms), and in γ-methylene groups—there are three peaks with an area ratio of 3:6:6. In this case the carbonium ion, of course, cannot adopt a normal planar configuration characteristic of it. The same situation is observed with all the carbonium ions of bicyclic compounds in which the positive charge is on the bridgehead carbon atom.

Unstable Carbonium Ions. When olefins (and also tertiary alcohols) react with concentrated sulphuric acid, an equilibrium of the following type sets in:



in which the carbonium ion undergoes isomerization (see below) and can also enter into synthetic reactions, such as the Koch reaction involving carbon monoxide (page 241, and also Volume I, page 213) or the alkylation of alkanes.

Unstable alkyl cations are also formed by the ionization of tosylates (*p*-toluenesulphonate esters) of tertiary alcohols in a medium, say, of glacial acetic acid:



Alkyl cations can be prepared by the oxidative decarboxylation of carboxylic acids, say, by the action of lead tetraacetate on the

acids:

$$2RCOO^- + Pb(CH_3COO)_4 \longrightarrow 2R^+ + 2CO_2 + Pb(CH_3COO)_2 + 2CH_3COO^-$$

Finally, when the amines are acted on by nitrous acid, the reaction proceeds through the stages of formation of a diazonium ion and then of a carbonium ion after the elimination of the nitrogen molecule, which accounts for the numerous isomerization reactions that accompany the Demyanov reaction (page 286), and also for the formation of a double bond.

The usual conversion of the alkyl (or cycloalkyl) cation into an olefin by ejection of a proton

$$\overset{+}{R}CHCH_3 \longrightarrow R-CH=CH_2 + H^+$$

is exactly the same conversion that takes place reversibly in concentrated sulphuric acid. The breakdown of an aromatic diazonium salt which occurs if there is involved the anion of a strong acid, say, BF_4^-, also proceeds with the intermediate formation of an aryl cation:

$$C_6H_5\overset{+}{N}_2\ BF_4^- \longrightarrow C_6H_5^+ + N_2 + BF_4^-$$

Reactions of Aryl Cations. An aryl cation can be fixed by the addition of any anion, and also of oxygen to a free pair of electrons, say, in $(C_6H_5)_2O$, or a halogen in chloro- or bromobenzene, with the formation of the respective cations

$$(C_6H_5)_3\overset{+}{O} \quad (C_6H_5)_2\overset{+}{Cl} \quad (C_6H_5)_2\overset{+}{Br}$$

The $C_6H_5^+$ cation can also be detected as an electrophilic reagent upon entry into the benzene ring at the *meta*-position to *meta*-directors (A. N. Nesmeyanov, T. P. Tolstaya, L. G. Makarova, L. S. Isaeva).

Reactions of Alkyl Cations. It has already been said that one of the ordinary reactions of alkyl cations is the ejection of a proton and conversion into an olefin. This reaction cannot, of course, be shown by the methyl cation and cations that bear a positive charge on the tertiary carbon atom of a bicyclic compound (by virtue of Bredt's rule which states that no double bond can be formed at the bridgehead).

Alkyl cations react with strong anions (i.e., anions of weak acids), recombining into molecules

$$R^+ + A^- \longrightarrow RA$$

and interact with protic solvents, displacing the proton; for example,

$$R^+ + H_2O \longrightarrow ROH + H^+$$

As a matter of fact, reactions of the latter type also include the alkylation of alkanes, a reaction in which the ejection of a proton is effected more difficultly and which requires the participation of an agent capable of assisting this elimination. For instance, when an olefin is reacted in the presence of liquid hydrogen fluoride with alkanes, the reaction proceeds through the stage of formation of an alkyl cation (the olefin adds a proton). This cation alkylates the tertiary or secondary carbon atom in the alkane, from which HF removes the proton in the form of $[H_2F]^+$.

Alkyl cations are capable of adding carbon monoxide (the Koch reaction). This reaction is effected by the direct action on a solution of an olefin in sulphuric or any other strong acid of carbon monoxide or (as Koch did originally) of formic acid which decomposes according to the equation:

$$HCOOH + H_2SO_4 \longrightarrow CO + H_2O \cdot H_2SO_4$$

The Koch reaction, as a whole, proceeds by the following scheme:

$$R-CH=CH_2 + H^+ \longrightarrow R-\overset{+}{C}H-CH_3$$

$$R-\overset{+}{C}H-CH_3 \xrightarrow{+CO}$$

$$\longrightarrow \left[R-CH-CH_3 \leftrightarrow R-CH-CH_3 \right] \xrightarrow[-H^+]{+H_2O} R-CH-CH_3$$

$$\left[{}^{+}C=O \qquad\qquad C\equiv O^+ \right] \qquad\qquad HO-C=O$$

Acylium cation

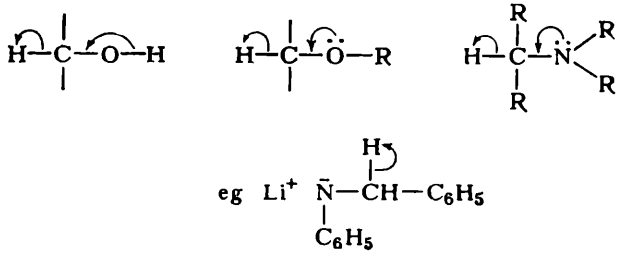
The addition of carbon monoxide to the carbonium ion gives the acylium cation capable of existence in concentrated sulphuric acid or in the form of salts with such anions as BF_4^- and $SbCl_6^-$. We have already encountered the acylium cation in describing the derivatives of carboxylic acids (see Volume I, page 224) and in considering the hydrolysis of esters by the S_N1 mechanism (see Volume III, page 211).

17.1. Hydride Shifts

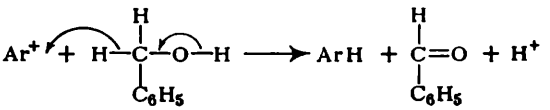
Carbonium ions are capable of capturing the hydride ion, i.e., hydrogen with a pair of bonding electrons ($H:^-$). Such reactions are called **hydride shifts** (hydride transfer reactions). These reactions may proceed intermolecularly or intramolecularly.

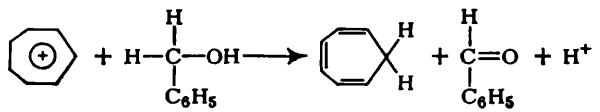
In intermolecular hydride shifts, the hydride-ion acceptor is a carbonium ion and the role of the donor is played by the group-

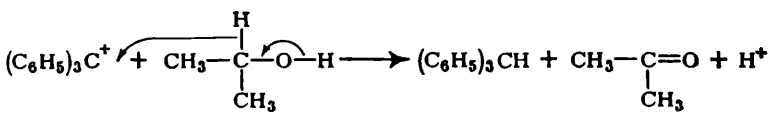
ings



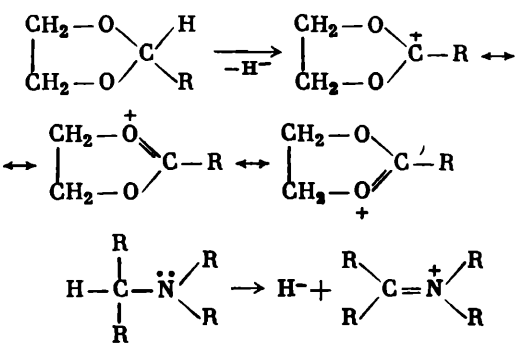
Such reactions may be illustrated by the example of an alcohol functioning as the hydride-ion donor:

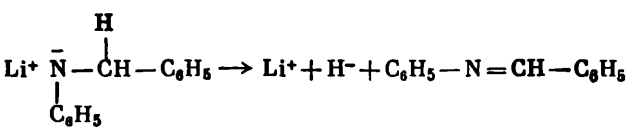






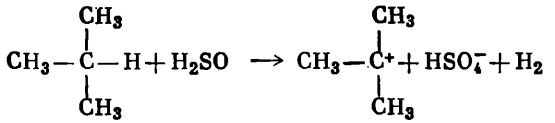
Analogously, other donors, giving H^-, are converted as follows:



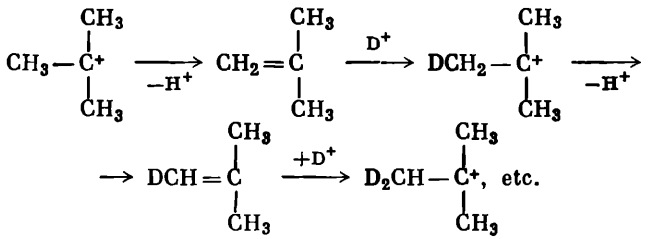


The last one is the strongest hydride-ion donor. It gives a hydride ion not only to true carbonium ions but even to ketones, the hydride ion being added to their carbonyl carbon.

D. N. Kursanov, V. N. Setkina, and Z. N. Parnes have found that hydrocarbons that have a tertiary carbon atom exchange their total hydrogen for deuterium in concentrated deuterosulphuric acid. The first stage is the oxidation by sulphuric acid of the tertiary carbon atom to a relatively stable tertiary carbonium ion:



Then the carbonium ion gradually exchanges all its hydrogens for deuterium, due probably to the ejection of a proton and addition of a deuteron to the olefin formed:



As a result of the hydride shift a positive charge appears on the carbon atom from which the hydride ion has migrated. This carbon atom now plays the role of the carbonium ion. The data given in Table 17 2 show that tertiary carbonium ions are energetically the

TABLE 17.2. **Energies of Conversion $R\cdot + e^- \rightarrow R^+ + 2e^-$ and Heats of Formation of Carbonium Ions (e^- is an electron)**

R^+	Ionization potential of radical	Relative energy of radical conversion, kcal/mole	Heat of formation of ion, ΔH_f, kcal/mole
CH_3^+	—	—	262
$CH_3CH_2^+$	—	—	224
$CH_3CH_2CH_2^+$	8.69	29.2	216
$CH_3\overset{+}{C}HCH_3$	7.90	11.1	190
$CH_3CH_2CH_2CH_2^+$	8.64	28.1	207
$(CH_3)_2CHCH_2^+$	8.35	21.4	211
$CH_3CH_2\overset{+}{C}HCH_3$	7.93	11.7	181
$(CH_3)_2\overset{+}{C}CH_3$	7.42	0	166

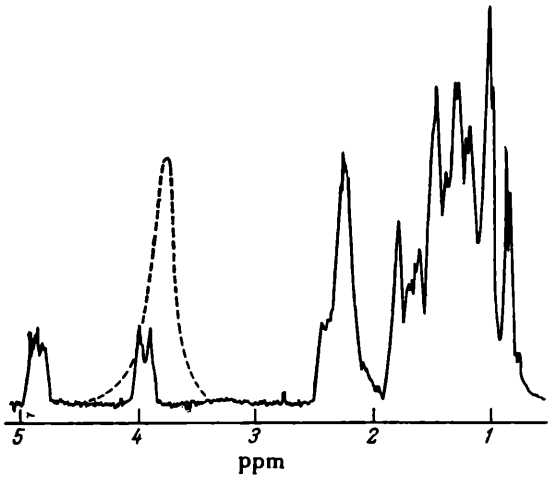


Fig. 17.3.

The NMR spectrum of norbornyl fluoride in a solution of CCl_4 (heavy lines) and of the norbornyl cation formed from it by the action of SbF_5 (broken lines).

most stable and primary carbonium ions the least stable. Therefore hydride shifts occur in a direction that leads to the preponderance of tertiary carbonium ions in the equilibrium mixture of alkyl cations, the amount of secondary carbonium ions being less and that of primary ones the least. The shifts given below are exothermic:

primary $\longrightarrow$ secondary $\longrightarrow$ tertiary

Intramolecular hydride shifts are also possible. For instance, according to O. A. Reutov and T. N. Shatkina, when nitrous acid acts on 1-propylamine labelled at carbon 1, a mixture of 1-propanol-^{13}C and 3-propanol-^{13}C is formed (of course, along with isopropyl alcohol):

$$CH_3-CH_2-{}^{13}CH_2-NH_2 \xrightarrow[-N_2]{HNO_2}$$

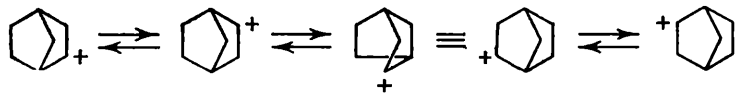
$$\longrightarrow CH_3-CH_2-\overset{+}{{}^{13}CH_2} \xrightarrow[-H^+]{+H_2O} CH_3-CH_2-{}^{13}CH_2OH$$

$$\Big\downarrow \text{1-3 hydride shift}$$

$$\overset{+}{C}H_2-CH_2-{}^{13}CH_3 \xrightarrow[-H^+]{+H_2O} HOCH_2-CH_2-{}^{13}CH_3$$

Such a 1-3 hydride shift is possibly the result of two 1-2 hydride shifts. Another intramolecular 1-2 hydride shift has been observed by Olah. He has found that if norbornyl fluoride is dissolved at 20°C in antimony pentafluoride, the NMR spectrum changes from the complex one shown in Fig. 17.3 by a heavy line to a simple peak

(the broken line), which indicates that all the hydrogen atoms in the norbornyl cation are identical. This can be understood only if it is assumed that a fast 1-2 hydride shift and a fast Wagner retropinacol rearrangement (page 276) take place simultaneously, which average the picture:



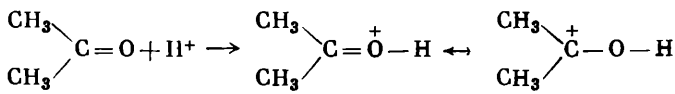
The last scheme is also reminiscent of the rearrangements of carbonium ions which have already been discussed and will be treated in more detail in Chapter 20.

According to Olah, when dissolved in the super-acid $HSO_3F + SbF_5$ methane (under pressure, at 140 °C) captures a proton, forming the **methonium ion** CH_5^+, whose generation by the action of a proton on methane was discovered by V. L. Tal'roze by means of a mass-spectrograph. Under the conditions of the experiment the methonium ion is unstable and breaks down into a carbonium ion and molecular hydrogen:

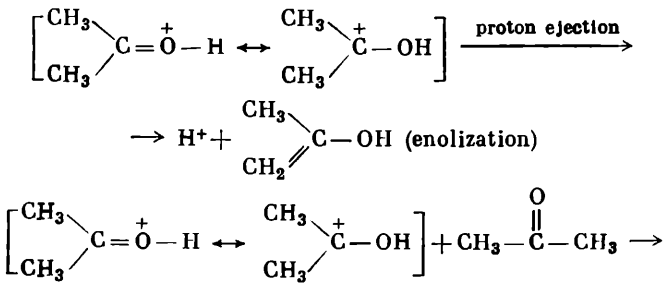
$$CH_5^+ \longrightarrow CH_3^+ + H_2$$

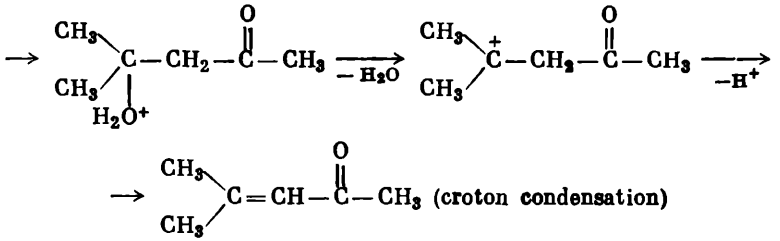
In other words, the proton pulls out a hydride ion from methane. Analogously, according to Olah, other saturated hydrocarbons are also capable of capturing the proton of "super-acids" and of undergoing the conversions described above.

Carbonyl compounds in acid medium accept a proton on their carbonyl oxygen, and their carbon atom becomes partially a carbonium carbon with the positive charge delocalized between the carbonyl carbon and oxygen of the carbonyl compound:



Therefore, aldehydes and ketones in acid medium behave as carbonium ions in certain reactions; for example:





Here mention should be made of the stable acylium ions formed by the action of Lewis acids or concentrated H_2SO_4 on acid halides of carboxylic acids (or, accordingly, their esters) (Seel):

$$R-\underset{\underset{O}{\|}}{C}F+BF_3 \longrightarrow [R-\overset{+}{C}=O \leftrightarrow R-C\equiv\overset{+}{O}]\ BF_4^-$$

$$R-\underset{\underset{O}{\|}}{C}-Cl+SbCl_5 \longrightarrow [R-\overset{+}{C}=O \leftrightarrow R-C\equiv\overset{+}{O}]\ SbCl_6^-$$

The structure of **acylium cations** is characterized by the delocalization of the positive charge between oxygen and carbon.

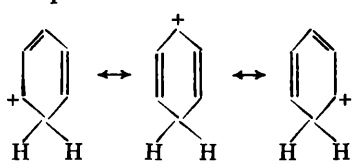
Acylium cations are important intermediates in the acid hydrolysis of esters (Volume III, page 211) and in other reactions of the derivatives of carboxylic acids.

Carbonium ions of a different type are formed in the protonation of aromatic hydrocarbons. Although aromatic hydrocarbons are very weak bases, nevertheless under certain conditions they are able to enter into acid-base interaction with proton acids. For example, when benzene, toluene, naphthalene and all polycyclic aromatic hydrocarbons with fused rings are dissolved in liquid hydrogen fluoride, an equilibrium sets in:

$$ArH+HF \rightleftarrows ArH_2^+ + F^-$$

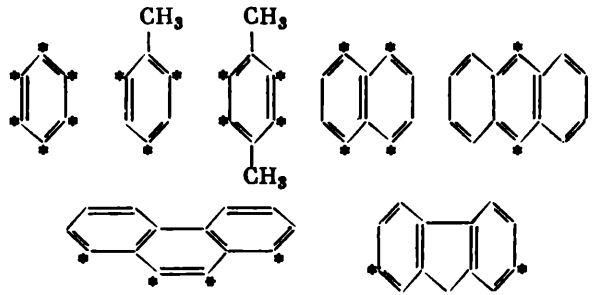
which can be markedly shifted to the right by addition, say, of boron trifluoride, which binds the fluoride ion into the stable BF_4^- anion.

According to spectral data, this results in the formation of σ-complexes; for example:

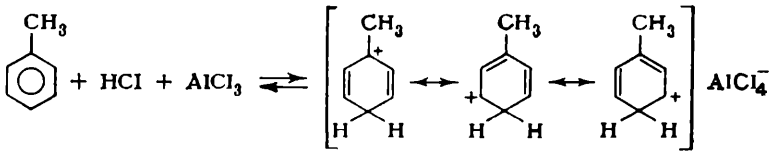


in which the carbonium charge is delocalized over the *ortho-* and *para*-positions of the ring. In the following formulas, the asterisks denote the possible sites of protonation, i.e., the sites of the highest

basicity:



The conducting coloured solutions being formed at a low temperature in a system consisting of an aromatic hydrocarbon, hydrogen chloride, and aluminium chloride, also contain carbonium salts of halogenoaluminium acids. For example, at —80°C aluminium chloride dissolves in toluene when HCl is passed into the mixture; this gives a green solution containing carbonium ions:



Chapter 18

Mechanisms of Chemical Reactions

We have already met with the division of reactions into homolytic and heterolytic reactions and with the classification of the latter into nucleophilic and electrophilic substitutions (see Volume I, page 31). For each of these types there are possible kinetic subtypes of first- and second-order reactions. Using this classification of Ingold and his own symbolism, we have four principal types of heterolytic substitution reactions: S_N1, S_N2, S_E1, S_E2. In these designations, the letter S denotes a substitution reaction, N and E signify, respectively, nucleophilic and electrophilic, and the numbers indicate the kinetic order of the reaction.

The following two types should also be added to these principal types: S_Ni and S_Ei (i stands for intramolecular), which mean an intramolecular nucleophilic and an electrophilic substitution reaction. By definition, these are invariably first-order reactions, i.e., intramolecular heterolytic rearrangements (see Chapter 20).

There are also possible exchange reactions which proceed according to the following scheme:

$$AX+BY \longrightarrow \left[\begin{matrix} A-X \\ \vdots \quad \vdots \\ Y-B \end{matrix}\right] \longrightarrow AY+BX$$

when both parts of the molecule AX simultaneously attack the two parts of the molecule BY, i.e., the exchange takes place through a four-centre (four-membered) transition state. This type of substitution reactions is sometimes designated as S_F (F stands for four). It is obvious that this is a reaction of the second kinetic order.

Reactions of heterolytic addition, Ad, across a multiple bond may also be classified as the nucleophilic, Ad_N, or electrophilic, Ad_E, initial attack on the multiple bond. A simultaneous attack of the type

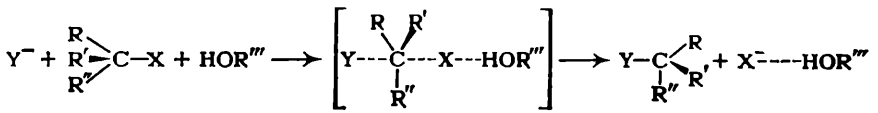
$$A=B+X-Y \longrightarrow \left[\begin{matrix} A-B \\ \vdots \quad \vdots \\ X-Y \end{matrix}\right] \longrightarrow \begin{matrix} A-B \\ | \quad | \\ X \quad Y \end{matrix}$$

is also possible here, which proceeds through a four-centre transition state and is denoted as Ad_E. This is invariably a second-order reaction.

And, lastly, one more type of reactions, which has not yet been mentioned, is elimination reactions which are denoted by E and which are often the reverse of the Ad type. Since, however, the elimination of X—Y from

with the formation of A=B can be accomplished without the action of a reagent and can proceed monomolecularly, this is the E_1 type. If it is necessary that X or Y be attacked by a reagent (which may be either nucleophilic or electrophilic), the elimination reaction proceeds as a second-order reaction and is designated as E_2.

As a matter of fact, the classification given is only a very simplified scheme. Reactions often involve a third and, sometimes, a fourth particle and third- and fourth-order reactions and also reactions of mixed orders are formally not rare. In some cases the third particle is a solvent and in other this is the reagent itself. More often than not, the participation of a third particle is manifested by the pull-push principle; for example:



Sometimes, it takes part in a cyclic transition state, examples of which can be found in the following section.

18.1. The Structure of the Transition State

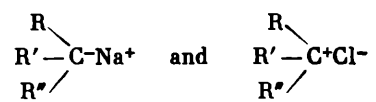
We have already considered (see Volume I, page 109) the physical chemistry of the transition state (the activated complex). The student who takes up a study of organic chemistry must realize the importance of a knowledge of the parameters of the transition state of a given reaction for the quantitative prediction of its course. Up to the present time, however, there have been no methods of elucidating the structure of the activated complex, similar to the reliable chemical and physical methods used for the determination of the structural formulas of ordinary molecules. This is accounted for by the fact that the concentration of the invariably unstable transition state, which is at an energy maximum ("hump"), is vanishingly low as

compared with the remaining part of the reaction mass, and the activated complex can be neither separated from it nor characterized. Although one can hope that the rapidly developing electron-paramagnetic-resonance and nuclear-magnetic-resonance (EPR and NMR) methods and also optical methods will contribute to the knowledge of the structure of the transition state, at present we have to derive formulas for the transition state by indirect means, on the basis of data on the stereochemical course of the reaction, its kinetics in various solvents and their mixtures, on the use of the isotope effect, and on the energy and geometry considerations. Finally, the Hammond postulate is very useful.

The first question as to the number of molecules of this or that reagent participating in the structure of the transition state is solved on the basis of the reaction order with respect to each of the reagents.* If the compounds AB and CD are involved in the reaction and the reaction rate is proportional to the concentration of each of them, i.e., to the product [AB] [CD], then it is a second-order reaction (first-order in each of the reactants), and the transition state involves one molecule of each of the reactants. If the reaction rate is proportional to the product [AB] $[CD]^2$, the reaction being third-order, then one molecule of AD and two molecules of CD will take part in the transition state, etc. (see the footnote).

The stereochemical course of the reaction, say, the retention of the configuration around the tetrahedral carbon atom being attacked (by a nucleophile or electrophile), or a Walden inversion, provides an answer to the question as to from which side—from the side of the leaving group or from the opposite side—the attacking particle is approaching.

The first order of the reaction with respect to one of the reactants and the zero order with respect to the other is evidence of the preliminary dissociation of this reactant, which usually takes place slowly and therefore determines the overall rate of the reaction. In this case, racemization often occurs provided, of course, that we are speaking of the substitution at an asymmetric tetrahedral carbon atom. The transition state in this case involves a particle of the dissociated molecule (an ion) and the molecule of the second reactant. If the ionized substance retains an unshared ion pair (in a nonpolar non-solvating solvent), then, for example, the cation and the anion in the examples



* This statement is rigorous only in application to reactions proceeding in one step or to an elementary step of a complex reaction.

will shield the ion-partner, and racemization (at least, complete will not occur—the optical activity is retained. Racemization often does not take place (or it is not complete) if the solvent molecule is involved in the reaction (which is, as a rule, disregarded kinetically since with a large excess of the solvent its concentration is practically constant), in which case it shields the ionic centre. Replacing the solvent or diluting it strongly with an inert solvent, it is possible, by varying the concentration, to reveal the participation of this solvent in the transition state.

The isotope effect is mainly used in the case of hydrogen and deuterium. If we have two compounds of identical structure, with the only difference that in one of them one or more hydrogen atoms are replaced by deuterium and it is exactly this atom (or atoms) is involved in the reaction and participates in the structure of the transition state, there is observed a sharp difference in the rate of the reaction of the hydrogen and deuterated compound. This is what is known as the **isotope effect.** The deuterium atoms that are not involved in the transition complex have no marked effect on the reaction rate (for an example, see Volume I, page 169, the oxidation of alcohols).

Hammond's postulate consists in the following. As has already been pointed out (see Volume I, page 120), the transition state, which structurally contains two (or more) reacting particles (molecules, ions, free radicals), has a maximum of energy and corresponds to the peak of the hump on the curve of the system energy (the ordinate) versus the reaction coordinate (the abscissa).

The **reaction coordinate** is a measure of the distances between the atoms—the major participants of the reactions.

If the reaction proceeds in several stages, each of them has a transition state with its own maximum. In order to raise the energy level of the reacting particles up to the transition state, it is necessary that the activation energy E be consumed (in the Arrhenius equation

$$k = Ae^{-\frac{E}{RT}}$$

where k is the reaction rate constant, T is the temperature, A is the pre-exponential factor).

When two free radicals or two ions are brought into reaction, the energy of activation is low if not equal to zero (i.e., equal to a few kilocalories per mole). If such an unstable particle reacts with a molecule, the activation energy is higher, but usually not great. But if two molecules react with each other and the reaction proceeds with a velocity measurable at ordinary temperatures, the activation energy is considerably higher and usually amounts to 15-30 kcal/mole. These cases can be represented schematically by three curves according to Hammond (Fig. 18.1).

The curve A on transition from the starting compounds to the maximum corresponds to the low energy of the rise and then to the deep energy fall down to the energy of the reaction products. Hence, energy-rich particles react here, the reaction involving, for example, an ion or ions. This is an exothermic reaction. The curve B has an opposite character: the rise is high and the fall is low, and energy-rich products are obtained. The reaction is endothermic. The curve C corresponds to a rather high rise and a rather deep fall, but it is more symmetrical than the previous ones and is typical of a reaction between two stable molecules (a second-order reaction).

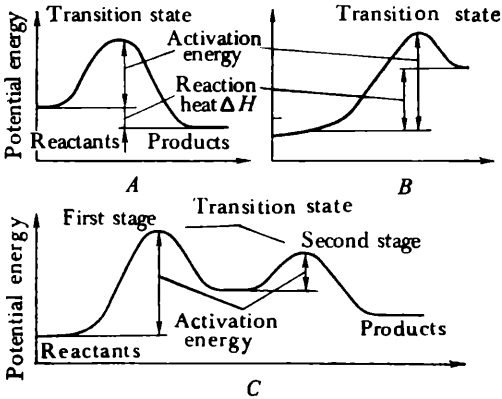


Fig. 18.1.

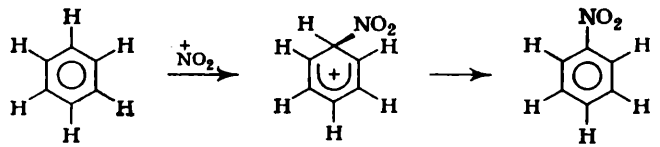
The energy state of reacting systems:
A—exothermic reaction; B—endothermic reaction; C—two-stage reaction.

It should be said that the curve A, for example, which represents the reaction between an ion and a molecule, i.e., a S_N (or S_E) reaction, has basically two humps, but the first, left-hand hump is omitted here—it represents the transition state of dissociation.

Hammond's postulate states that the transition state in its structure (i.e., in interatomic distances and angles, in short, in its geometry) is close in the case of A to the starting particles, and in the case of B, to the final products. This virtually justified postulate is based on the reasoning that once the energy of the initial state differs little from the maximum, the changes as compared with the initial state are not great. Such reasoning for the case B makes the transition state similar to the reaction products.

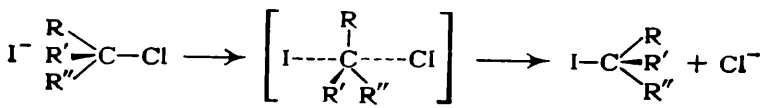
Finally, of great importance are purely geometric considerations. All the interatomic distances in the activated complex are the same ordinary distances, except the lengths of the bonds made and broken, both of which exceed but little ordinary covalent distances. The

valence angles also change at atoms that are linked and at bond-breaking atoms in accordance with the new hybridization state of electron orbitals. For instance, in the case of the electrophilic displacement of hydrogen in benzene

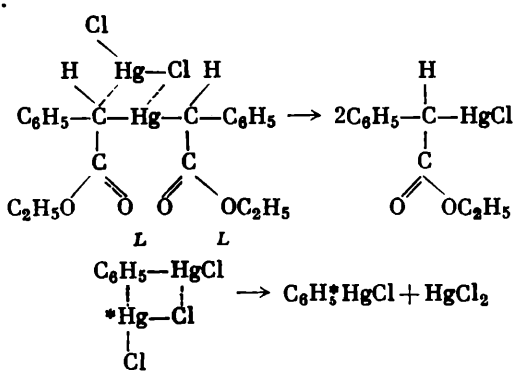


the attacked carbon in the activated complex is transferred from the sp^2-hybridized state (the second valence state) to the sp^3-hybridized state (the first valence state—the tetrahedral carbon) and tends to change the valence angles from 120 to 109°.

Just as in this case, we have often encountered the activated complexes of the simplest structures and we know that, for example, the S_N2 nucleophilic substitution at the tetrahedral carbon occurs through the transition state shown below, which is what accounts for the Walden inversion:

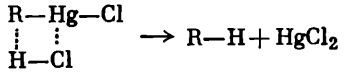


Since in S_E2 reactions, which have been studied much less, there is usually observed retention of configuration, it is obvious that in the transition state the attacking electrophilic species approaches from the side of the group being replaced. For example, the reactions of organomercury compounds studied by O. A. Reutov are therefore believed to involve a four-centre (four-membered) cyclic transition state:



where *Hg is the radioactive isotope of mercury.

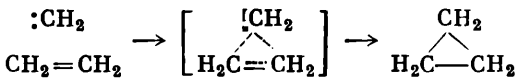
Such a four-centre transition state is also assumed (Reutov and Dessy) for the case of the decomposition of an organomercury compound by an alcoholic solution of hydrochloric acid:



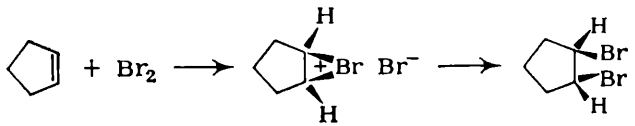
Indeed, the rate of decomposition of organomercury compounds by hydrochloric acid is much higher than with oxygen-containing acids under the same conditions, which is what leads us to assume the involvement of chlorine in the transition state.

Even for these simplest reactions we have to assume cyclic transition states, which are believed to be four-centre in this case. Cyclic activated complexes are a very widespread phenomenon in chemistry.

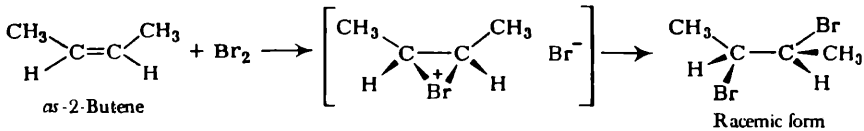
Numerous reactions of addition of carbenes at a multiple bond (see page 230) probably occur through a **three-centre (three-membered) transition state**:



The electrophilic attack of bromine on an olefinic double bond proceeds, as has already been pointed out (see Volume II, page 52), through the three-membered bromonium cation. This is proved by the fact that in cycloolefins bromine adds in the *trans*-position:

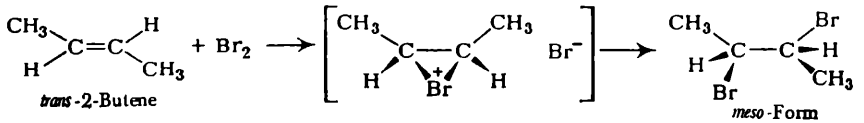


The three-membered bromonium ring is attacked by the bromide ion and is opened with a Walden inversion, which explains why the bromine atoms are found to be in the *trans*-position to each other. For this phenomenon to be observed in the aliphatic series such an olefin must be chosen, whose bromination would give rise to an asymmetric atom. Such is the case of bromination of two geometric isomers of 2-butene:



as-2-Butene

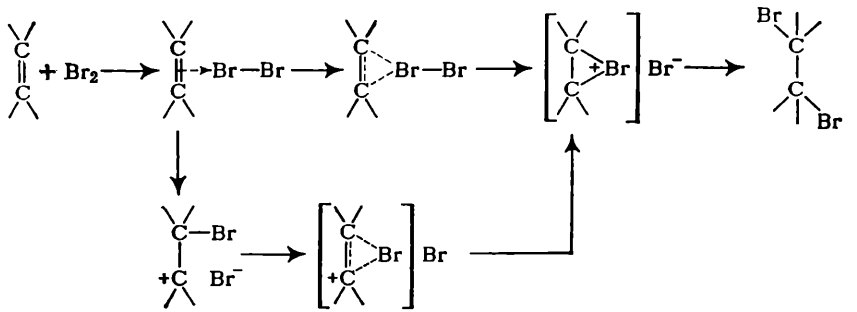
Racemic form



trans-2-Butene

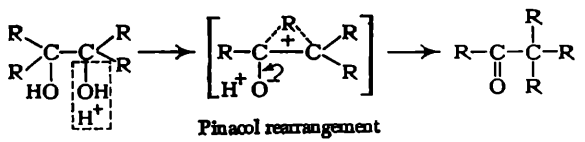
meso-Form

The formation of an unstable three-membered bromonium ring is apparently preceded by the stage of formation of a π-complex of an olefin with a bromine molecule, which can be converted into bromonium by either of the two following pathways:

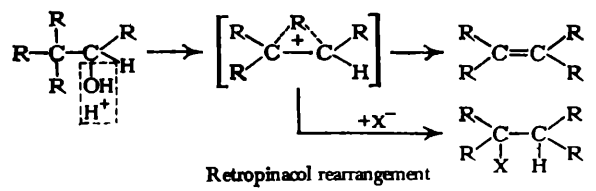


However that may be, with any of these routes the reaction must proceed via a three-centre transition state preceding the stage of the cyclic bromonium cation, and when the latter is opened by the bromide ion the reaction must give the effect of Walden inversion.

Numerous reactions of isomerization of the carbon skeleton, similar to the pinacol and retropinacol rearrangements (see pag 275 *et seq.*), also proceed via a three-centre transition state:



Pinacol rearrangement

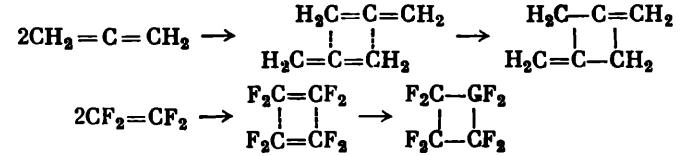


Retropinacol rearrangement

The absence of a carbonium ion in such processes has been proved by D. N. Kursanov by the fact that during the rearrangement the compound does not exchange its hydrogen for a deuterium from the medium (D_2SO_4, D_2O), as is typical of carbonium ions.

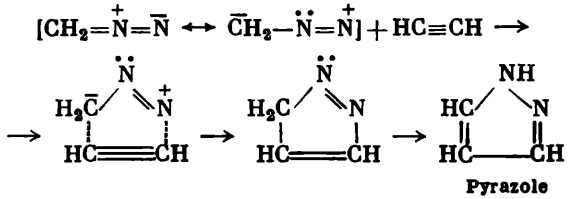
A four-centre (four-membered) transition state shows up in reactions of dimerization of allene and tetrafluoroethylene, which give rise

to cyclobutane derivatives:

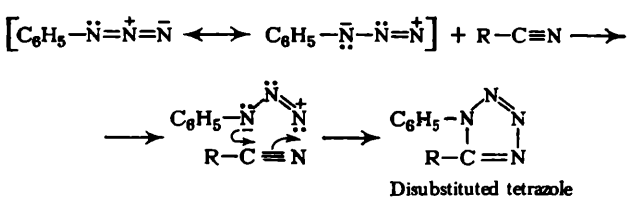


It is quite possible that the addition of organolithium and organomagnesium compounds to the carbonyl group also takes place through a four-centre transition state.

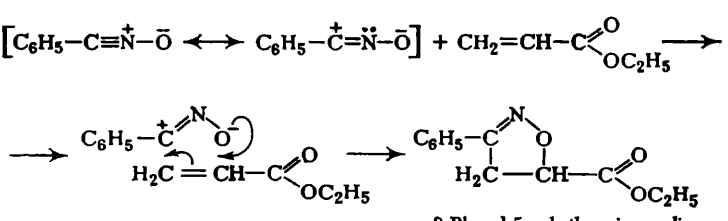
Numerous reactions of 1,3-dipolar addition to olefins, acetylenes, nitriles, etc. (Volume III, page 327), as has been proved by Huisgen, occur through a **five-centre transition state.** To clarify what is meant here, we shall give, once again, some examples of this type of cyclization:



Pyrazole



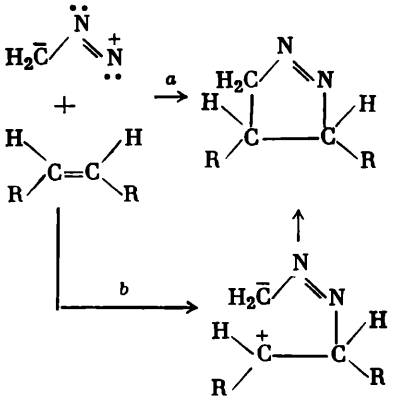
Disubstituted tetrazole



3-Phenyl-5-carbethoxyisoxazoline

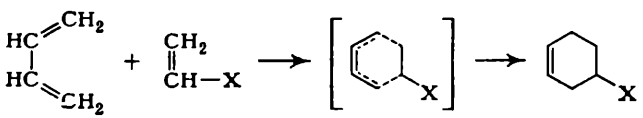
According to Huisgen, numerous such cyclization reactions proceed bimolecularly and stereospecifically. Thus, rings obtained, for example, from *cis*-diphenylethylene, have phenyl groups in the *cis*-position; the same stereospecificity is shown by reactions of *trans*-olefins. Two reaction mechanisms are conceivable. This may be illustrated by the addition of diazomethane to an olefin.

The following pathways are possible:



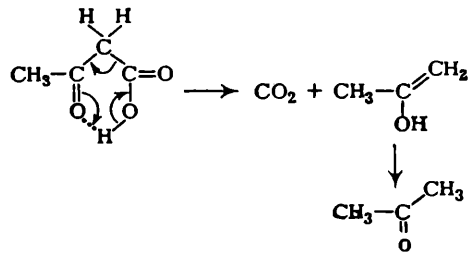
The pathway *a* presupposes a direct addition via a five-centre transition state, and the pathway *b* involves an addition in two stages, first by one of the dipole ends (by the terminal nitrogen of diazomethane, in this example), and then the ring-closure. Both processes must proceed as bimolecular reactions since the rate-determining (slow) processes must be the bimolecular reactions *a* and *b*. An argument against the pathway *b* is the practically identical rate of addition in media of sharply differing dielectric constants. The high dielectric constant of the medium will assist the step *b* since, as a result of this step there is formed a dipole with remote (+) and (—) charges separated by a saturated hydrocarbon unit. Besides, the high dielectric constant of the medium must contribute to ionization, decreasing the energy required. The pathway *a* is independent of the properties of the solvent. A second argument in favour of the pathway *a* is provided by the relatively low activation enthalpies and high activation entropies of processes of this kind, which is characteristic of a cyclic transition state, as will be shown at a later time.

As has been pointed out by Ya. K. Syrkin, especially widespread are **transition states with six centres.** It is quite obvious that these include the familiar Diels-Alder reactions, just as the Lebedev dimerization of dienes:

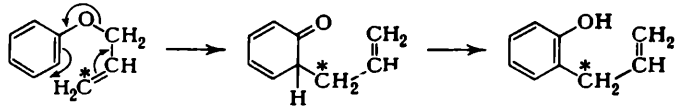


The decarboxylation of β-ketonic acids, as shown by Westheimer and Jones, occurs through a six-centre cyclic transition state and

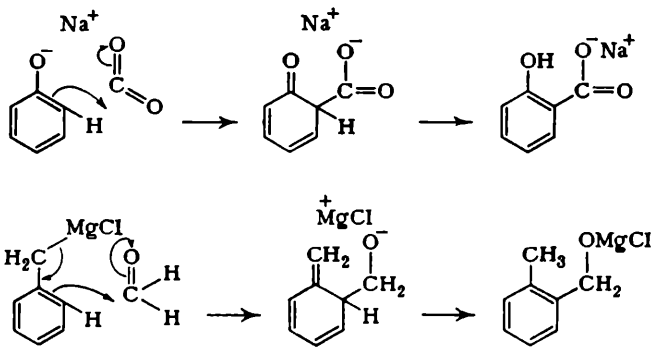
leads to the formation of the enols of ketones:



A six-centre cyclic transition state is also involved in the Claisen rearrangement of the allylic ether of phenol to *o*-allylphenol, which has been shown by the isotope exchange method to involve the attachment of the allyl group to the benzene ring via the γ-carbon atom:



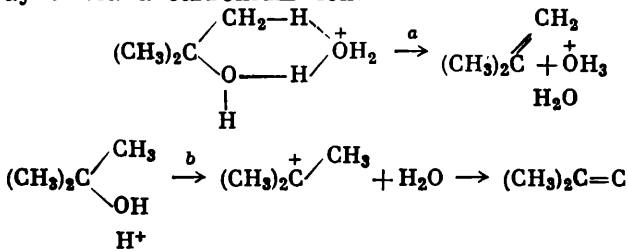
The Kolbe reaction and the abnormal reaction of benzylmagnesium chloride with formaldehyde explicitly proceed through a six-centre transition state (including an ion pair):



In these cases, particularly spectacular is the cyclic migration of electrons, which is generally typical of cyclic transition states.

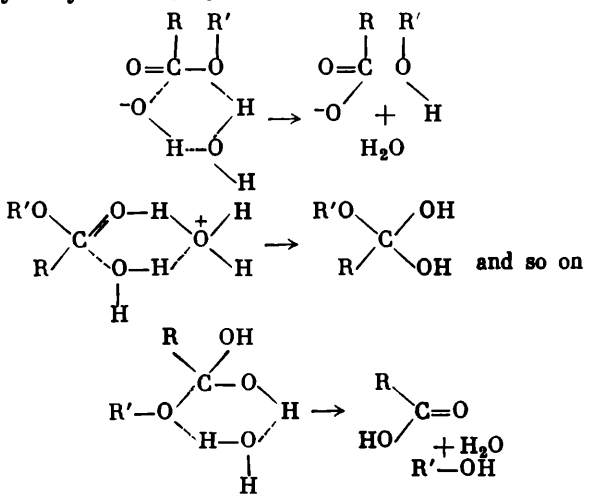
Syrkin believes that the course of many acid-base catalytic reactions is also accomplished through a six-centre activated complex. These include, for example, the dehydration of alcohols, in which the course of reaction *a* can successfully compete with reaction

pathway *b* via a carbonium ion:

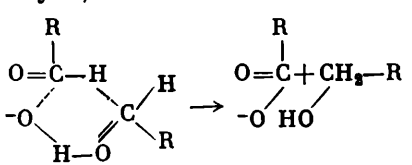


The formation of rings of the same kind with the participation of water, the hydroxonium cation or hydroxyl ions may also be assumed for many other processes of acid-base catalysis.

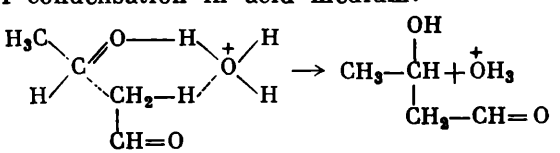
A cyclic transition state is suggested by Syrkin for the alkaline and acid hydrolysis of esters:



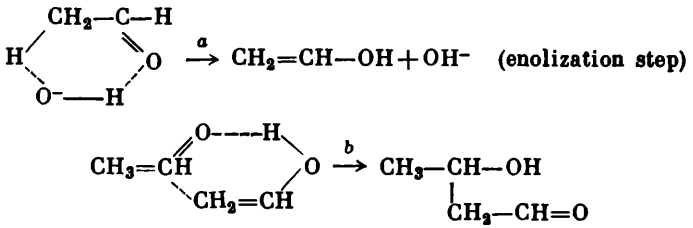
for the Cannizzaro reaction (which is third order; second order with respect to benzaldehyde, and first order in alkali)



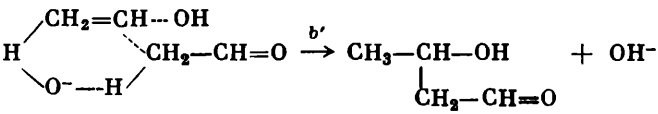
for the aldol condensation in acid medium:



and in alkaline medium



or



With suitable rates of the stages of enolization and condensat proper in the corresponding variants of the Syrkin method there be obtained third-order (in total) constants in the case (*a*-*b*) even fourth-order constants in the case (*a*-*b'*). In fact, the alkal aldolization gives orders intermediate between the third and fourth order. Of course, such cyclic activated complexes are noth more than hypotheses.

As seen from the schemes given, in the majority of reacti proceeding through cyclic transition states there takes place a tra fer of bonding electron pairs, which is synchronous throughout ring. Owing to this, the amount of energy consumed is natura reduced since no energy is required "in advance" for the cleav of the bonds of one or both reactants in order to convert them i energy-rich free radicals or ions. Even for this reason alone, energy of activation of a reaction occurring via a cyclic transit state is lower than that of the same reaction proceeding throu a complex other than a cyclic complex.

Recall that the rate constant k of the reaction proceeding a transition state is expressed by the formula:

$$k=\frac{\varkappa T}{h}\, e^{\frac{\Delta S^{\star}}{R}}\, e^{-\frac{\Delta H^{\star}}{RT}}$$

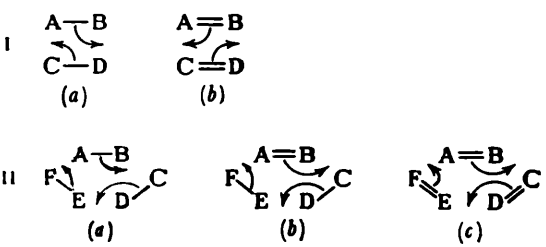
where T = temperature in °K; $\varkappa$, h, and R = constants; $\Delta S^{\star}$ $\Delta H^{\star}$ = entropy and enthalpy increments for the transition state compared with the initial state. The enthalpy increment in t case is very close to the activation energy. Thus, a decrease in $\Delta H^{\star}$ of the transition state sharply increases the rate of the re tion. In this lies the effect of the cyclic transition state. Accord

to Syrkin, this influence may be even stronger if the ring of the activated complex has quasi-aromatic character and, as a result of this, a lower energy content. The ring, however, in virtue of its structural rigidity, has a higher entropy (and, hence, a smaller probability) than a non-cyclic system. This factor operates in an opposite direction and in an exponential way too.

Energy considerations of this kind are supplemented by the reasoning as to the small probability of the participation in the reaction of particles, the formation of which requires a higher energy, for example, of unsolvated carbonium ions or carbanions, the elimination of H^+ from H_3O^+ and, in general, the preliminary cleavage (either homolytic or heterolytic) of strong bonds with a low energy level before the stage of formation of an activated complex. In this case, the $\Delta H^{\star}$ of the activated complex would immediately increase and the reaction rate would decrease to such values that the reaction would, in fact, stop.

It is easy to see that in cyclic processes taking place synchronously, like those described above, the boundary line between nucleophilic and electrophilic atoms becomes conditional and the concept of the reaction centre becomes less definite since several reaction centres appear simultaneously.

For this point to be illustrated, we have to cite once again the generalized schemes of reactions occurring via a cyclic transition state:



It is evident that in the cyclic activated complex each of the atoms involved—its units—is a reaction centre. The direction of electron pair transfers (the curved arrows) is mainly deduced on the basis of the relative electronegativities of the atoms. In scheme I*a* the arrow pointing to D is used because we know that D is more electropositive than B, and that A > C. Thus, B exerts in the ring a nucleophilic attack on D, and C attacks A. Since the energy effect of the reaction is independent of the route of the transition, it will be the same if it is assumed that there takes place a homolytic electron transfer rather than a transfer of electron pairs. For instance,

for scheme I*a* (the dashed arrows signify a one-electron transfer):

Schemes similar to I and II with a heterolytic migration of electrons are assumed, by analogy with non-cyclic transfers, to be similar processes by the mode of their occurrence. For example, the Kolbe reaction and, apparently, the analogous abnormal reaction of benzylmagnesium chloride with formaldehyde (page 258) are close to ordinary electrophilic substitution reactions in the aromatic ring and, hence, the transfer of electrons (their pairs) is analogous in all these reactions.

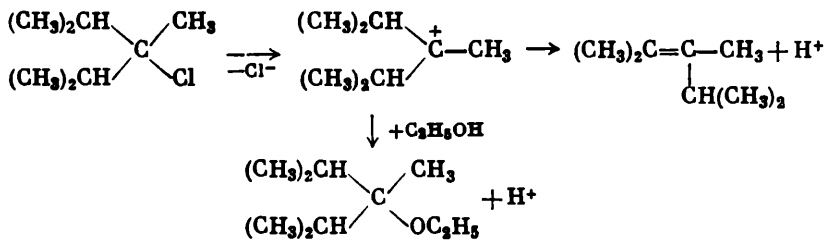
Chapter 19

Elimination Reactions

At the beginning of the sections on olefins and acetylenes we considered a number of reactions which are in a certain sense the reverse of additions at a multiple carbon-carbon bond. Such reactions are known as **β-eliminations.** Of especially great importance among numerous elimination reactions are the following: the elimination of hydrogen halides from monohalogeno derivatives and the Hofmann degradation, which is the elimination of water and a tertiary amine from quaternary ammonium hydroxides. Zaitsev's rule (1875) which refers to the first of these reactions states: the elimination of a hydrogen halide and the formation of a double bond occurs in such a manner that unsaturated carbon atoms carry the maximum possible number of alkyl groups.

In the Hofmann elimination, on the contrary, a hydrogen of a methyl group is preferably eliminated, so that in the majority of cases a $=CH_2$ group is formed.

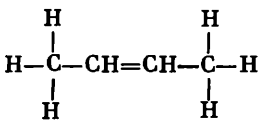
The kinetic studies carried out by Hughes and Ingold have established that, depending on the reaction conditions, the Zaitsev reaction may proceed in two ways. In strongly ionizing solvents, say, in alcohols (see Volume I, page 130), tertiary and, partly, also secondary halides are capable of slow electrolytic dissociation. A carbonium ion can then either join the anion or lose a proton and give an olefin. The two reactions compete with each other:



The elimination of a hydrogen halide, or **dehydrohalogenation,** is a monomolecular reaction. Its rate, just as the rate of solvolysis as a hole, is controlled by the rate of the slow ionization step. Such an elimination reaction is designated as *E*1.

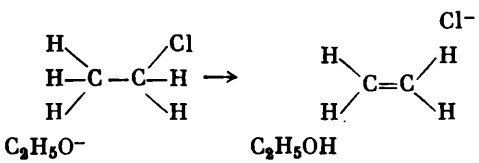
If the same halogen derivative is acted on by sodium alkoxide, the elimination reaction will proceed bimolecularly and will be denoted by *E*2. In this case, the reaction rate is proportional to both the concentration of the halogen derivative and the concentration of the alkoxide ion. The orientation is the same as before and obeys Zaitsev's rule.

The factor underlying Zaitsev's rule is the same as the one responsible for the migration of a double bond from the end to the centre of the molecule on passage of the olefin over a catalyst of the aluminium oxide type: thermodynamically stable are those olefins whose unsaturated atoms are linked to alkyl groups and not to hydrogens. Of importance here is the phenomenon of hyperconjugation, or σ,π-conjugation (see Volume II, page 88). Let us recall that in the system

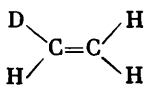


the σ-bonds of the methyl group are conjugated with the π-bond, and this entails a small decrease of energy.

It is interesting that the bimolecular elimination *E*2 proceeds, unlike *E*1 synchronously, i.e., the attack of the alkoxide ion on the β-hydrogen atom (β relative to the halogen) and its removal in the form of a proton takes place simultaneously with the ejection of the halide anion:



This has been proved by the fact that in a medium containing an exchangeable deuterium, say, in C_2H_5OD, the carbonium ion $\overline{C}H_2—CH_2Cl$, assuming that it existed for any perceptible period of time, must have entered into deutero-exchange and given $\overline{C}DH—CH_2Cl$. There would have been ejected Cl^- and, as a result, the deuterated ethylene



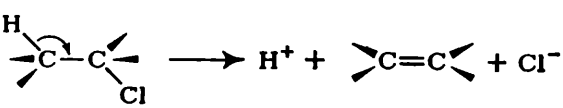
would be obtained as an impurity. In actual fact, pure ethylene is obtained, no deuterated ethylene being present in the product.

The Hofmann elimination is also a bimolecular reaction and belongs to the category of *E*2 eliminations. This mechanism operates in the destruction not only of quaternary ammonium hydroxides but of sulphonium and phosphonium hydroxides as well. In the case of the Hofmann elimination the base used is weaker (OH^- instead of OR^-) and the attack is exerted on the most easily replaceable hydrogen. For example, in the case of an ammonium base

$$R-\underset{\beta}{CH_2}-\underset{\alpha}{CH}(\overset{+}{N}(CH_3)_3)-\underset{\beta'}{CH_2}-H$$

the acidities of the hydrogen atoms α, β, β′ should be compared. Although the α-hydrogen atom is the most readily replaceable, its removal has nothing to do with the elimination of the $N(CH_3)_3$ group, just as, in general, with the degradation of the molecule: the capture of a proton from the medium immediately compensates for its loss and makes the molecule revert to its initial structure. Thus, the hydrogens β and β′ must be compared. If R is an alkyl, its $+I$ effect renders the β-hydrogen less acidic than is the β′-hydrogen. The attack is directed on the latter hydrogen atom and, as a result, there is formed an olefin $RCH_2CH=CH_2$ (an anti-Zaitsev olefin). If R exhibits a $-I$ or $-T$ effect, for example, if this is a halogen, a nitro group, or a benzene residue, the β-hydrogen atom will be more acidic, and the olefin will have the structure $R-CH=CH-CH_3$.

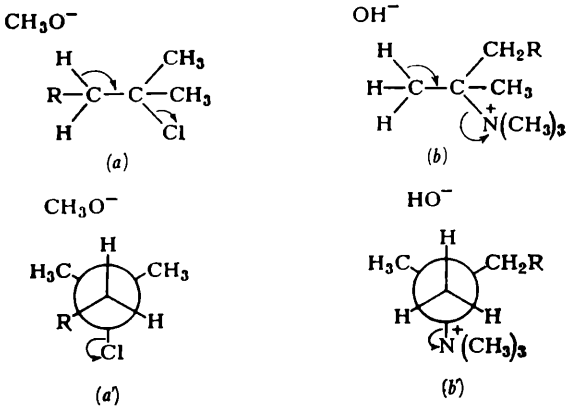
This interplay of polarities is not the sole factor that determines the direction of an elimination reaction. There is a second important one, the steric factor. It is more important in the Hofmann elimination since the NR_3 group is always more bulky than halogen. In the synchronous elimination, the molecule undergoing elimination invariably adopts in the transition state such a conformation that the proton being split off and the leaving atom or group [Cl or $N(CH_3)_3$] are in the *trans*-position. This is occasionally accounted for, by analogy with the Walden inversion, by the fact that the incoming substituent (the carbon atom being linked by a π-bond, in this particular case) must attach itself from the side opposite to the group being eliminated, NR_3 or Cl^-:



This explanation, however, is somewhat artificial.

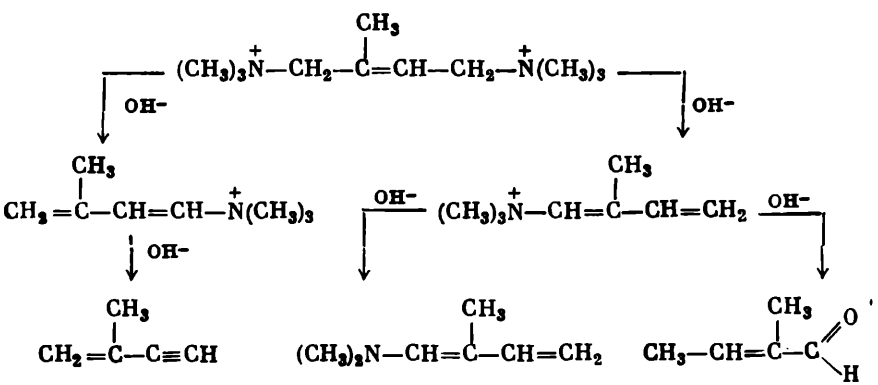
Taking $RCH_2C(CH_3)_2—X$ as an example, let us consider the transition states and steric hindrances in both types of elimination (along with ordinary formulas, their Newman projections are also given):

Zaitsev elimination *Hofmann elimination*

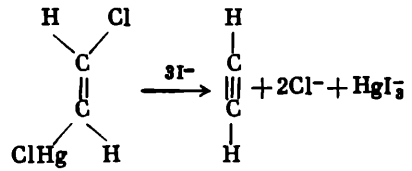


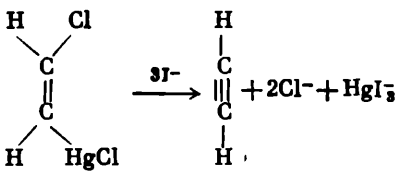
In the Zaitsev elimination, as seen from the projection *a'*, the R group, if it is bulky, hinders both CH_3 and the leaving group, the halogen; the steric hindrances would be even greater if the leaving group were the more bulky $N(CH_3)_3$. From the projection *b'* it is seen that with a different conformation of the transition state of the same compound there are no steric hindrances, and this aids the Hofmann orientation of elimination, the steric factor becoming more prominent in the case of the bulky group $N(CH_3)_3$.

Numerous elimination reactions of diammonium salts, in particular unsaturated ones, have been studied by A. T. Babayan. We shall consider one of the reactions which leads to propenylacetylene:



The requirement of the preferred *trans*-configuration of two leaving groups in the case of elimination from olefins changes to the requirement of the preferred *trans*-configuration of the leaving groups attached to unsaturated atoms. As an example may serve the elimination of HgCl and Cl from *trans*-chloromercurivinyl chloride, which has been studied by A. N. Nesmeyanov, A. E. Borisov, and I. S. Savelieva:

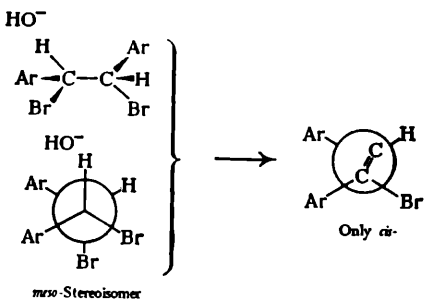


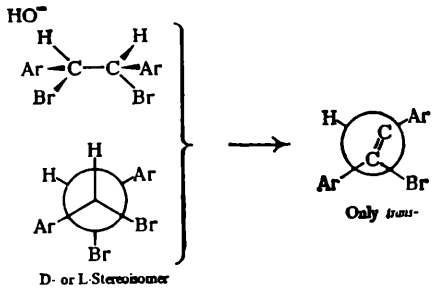


The *trans*-compound reacts considerably faster than does the *cis*-form. The authors attribute this to the more favourable steric conditions of the σ,σ-conjugation of the bonds Hg—C and C—Cl in the *trans*-compound. In fact, other reactions of elimination from olefinic carbon atoms also proceed more readily if the leaving groups have a *trans*-configuration.

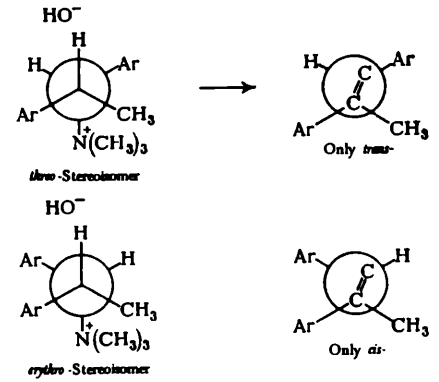
The following two examples show that the *trans*-elimination imposes such a conformation on the transition state that the elimination proceeds stereospecifically and the olefin produced is found to have a definite configuration, either the *cis*- or the *trans*-configuration.

Example 1:





Example 2:

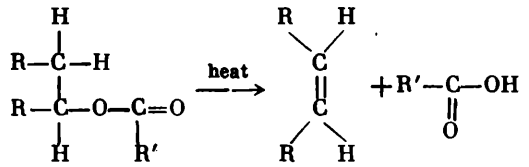


In example 2, the *threo*- and *erythro*-diastereomers of the compound $Ar(CH_3)CHCHAr\overset{+}{N}(CH_3)_3OH^-$ undergo the Hofmann elimination. Again, the elimination occurs in the conformation in which the hydrogen atom and $N(CH_3)_3$ group being eliminated are in the *trans*-position, and the elimination takes place stereospecifically: the *threo*-isomer forms only a *trans*-olefin, and the *erythro*-isomer gives its *cis*-counterpart. In the latter case, however, the reaction is slower by tens of times. Such a retardation is accounted for by steric hindrances in the transition state, which are created by two bulky aryl groups to each other, and by the necessity to overcome these hindrances at the expense of a higher activation energy.

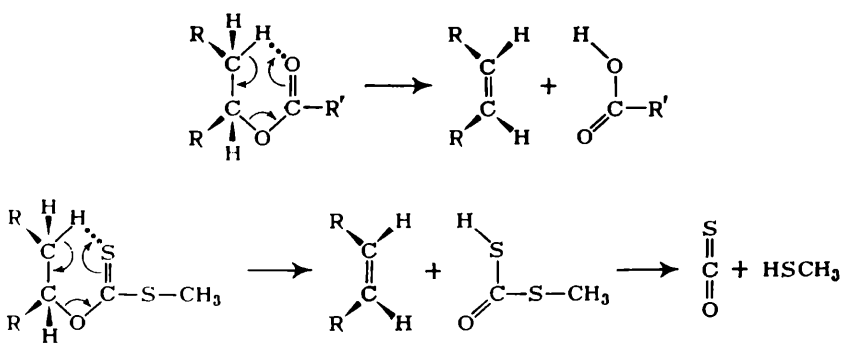
It is interesting to note that the pairs of compounds in examples 1 and 2 differ from each other by the opposite charges of one of the leaving groups [Br^- and $\overset{+}{N}(CH_3)_3$]. Hence, the requirement of the *trans*-arrangement of the groups being eliminated cannot be reduced to electrostatic factors.

Of the rarer *cis*-elimination reactions we shall cite the pyrolysis of carboxylate esters and the pyrolysis of the xanthate esters (the Chugaev reaction).

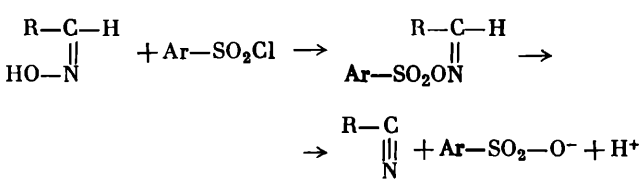
These reactions proceed by the following schemes:

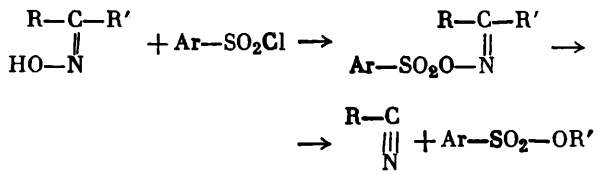


These two elimination reactions take place as first-order reactions and, hence, the elimination occurs intramolecularly. The negative activation entropy (see Volume I, page .119) indicates that the transition state formed is a more rigid structure than the starting material, i.e., a cyclization reaction has taken place. The following cyclic transition states (page 253 *et seq.*) have been suggested for the two reactions:



Elimination reactions are of course possible not only from carbon atoms. Examples of β-*trans*-eliminations have already been encountered. Recall the elimination of H and OH from *anti*- (i.e., *trans*-) aldoximes and the analogous Beckmann rearrangement of the second kind



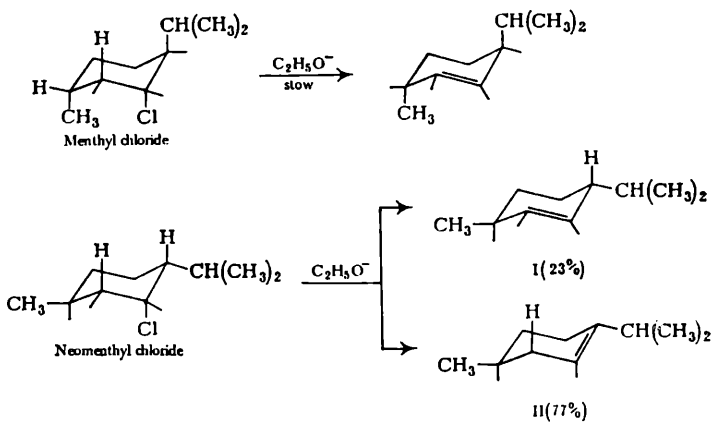


We have so far considered only β-eliminations. There exist, however, reactions involving the removal of two atoms or groups from the same carbon atom, or α-eliminations. These reactions usually lead to the formation of carbenes (page 228) or to the products of their rearrangement (page 292).

All that has been said about the occurrence of elimination reactions in open systems may also be applied to cyclic structures, but the specificity of the equatorial and axial positions of substituents imposes new requirements.

It is obvious that both groups to be eliminated must be in the 1,2-positions in the ring. If they are arranged in the *cis*-position, then one of them will inevitably be axial and the other, equatorial, i.e., they will not lie in the same plane, and the *E*2 reaction will not occur. But if the substituents are arranged *trans* to each other, then either both of them are equatorial or both are axial, the two conformations being readily interconvertible. The axial-axial conformation is favourable for an elimination reaction.

Below are given two examples of the dehydrochlorination of stereoisomeric chloro derivatives of the cyclohexane series—menthyl chloride and neomenthyl chloride (Ingold and Hughes):



Menthyl chloride may lose HCl in only one conformation in which H and Cl are axial and lie in the same plane (this conformation is

shown above). The change to this conformation is however hindered by the axial position of the isopropyl group—such bulky groups prefer an equatorial conformation, for which reason the reaction occurs slowly. With neomenthyl chloride, the situation is different: the conformation more favourable for elimination is stabilized by the equatorial position of the isopropyl group, and the reaction proceeds at a fast rate, predominantly to the side of formation of cyclo-olefin II.

Chapter 20

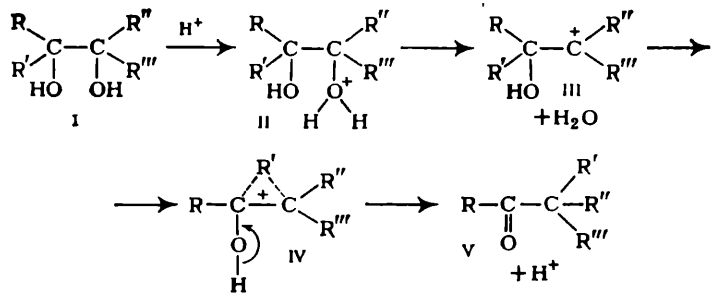
Rearrangements

The term "substitution reaction" implies that the substituent group takes the place of the group being replaced. This happens in the overwhelming majority of cases. The structure is changed only at the atom (or atoms) subjected to the attack of the reagent, the one at which the reaction takes place. This **rule of the least structural changes** serves as a guide in establishing the structure by chemical means. Exceptions to this rule are known, however, and we have already encountered such reactions in which the entering substituent takes the place not of the leaving group but of another atom, especially often, of the one adjacent to the atom from which the leaving group is removed. Such reactions called **rearrangements** caused a number of difficulties in structure elucidation, and attempts were of course made to ascribe these difficulties to the occurrence of these reactions through a number of such stages in which the principle of the least structural changes is not violated. These attempts, however, were found to be groundless, and many rearrangements were proved to occur intramolecularly in one step. The majority of rearrangements are heterolytic reactions.

20.1. Skeletal Rearrangements

We have already mentioned (see Volume I, page 139, and Volume II, page 247) the **pinacol-pinacolone rearrangement** (Fittig, Butlerov) which takes place when pinacols are acted on by acids, in particular, by Lewis acids. In a general form, this rearrangement

may be expressed as follows (R = hydrocarbon radicals):



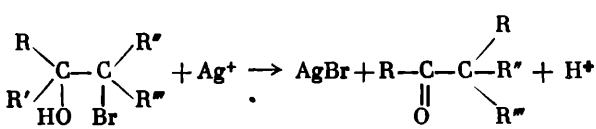
The division into steps is arbitrary here, given for more clarity. In actual fact, this is a concerted process, in which IV represents the transition state.

It has been established which radicals in this rearrangement migrate more readily (Tiffeneau, Orekhov, Bachmann). According to the ease of migration the radicals are arranged in the following sequence:

$$p\text{-}CH_3OC_6H_4 > p\text{-}CH_3C_6H_4 > C_6H_5 > p\text{-}ClC_6H_4 > \text{Alkyls} > H$$

The general conclusion is as follows: the most readily migrating is the radical which most strongly delocalizes the positive charge arising in the system as a result of the detachment of OH^- or, in other words, that radical migrates most readily which is most capable of undergoing electrophilic attack.

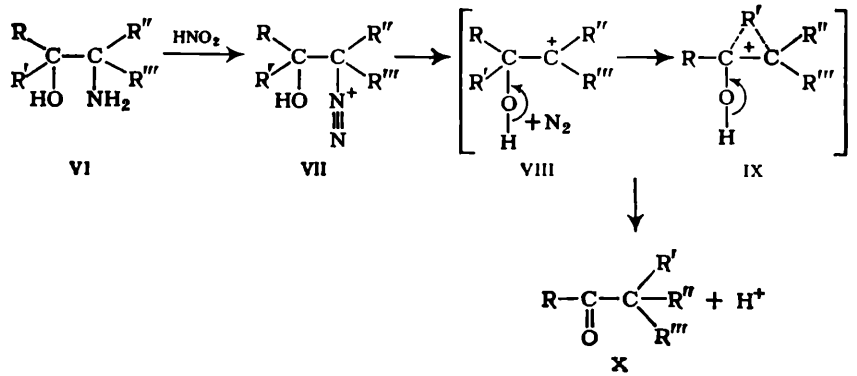
The fact that the initial moment of the rearrangement is the removal of the hydroxyl anion and the formation of a carbonium ion (which immediately delocalizes its charge in the transition state over the carbon atom from which the hydroxyl group has been detached, the neighbouring carbon atom of the skeleton and the key carbon atom of the migrating R′ group*) is proved by the following analogies:



(Only the starting bromohydrin and the end product pinacolone are given here; the mechanism is evidently the same as before.)

* Possibly, also inside the R′ group if it is unsaturated or aromatic.

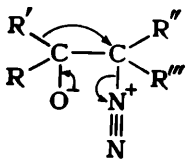
A further analogous rearrangement is the McKenzie oxidative deamination:



VI VII VIII IX X

The driving force of the reaction is the elimination of molecular nitrogen, and the contributing factor is the easy detachment of the proton from oxygen, which, in the long run, leads to the stable molecule.

The overall mechanism of the reaction may be formulated by a single scheme of synchronous conversion:



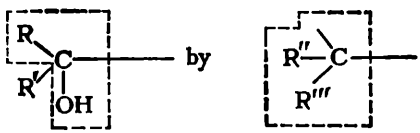
The oxidative deaminati ,n was also the first reaction to be used for establishing the stereochemical course of the pinacol rearrangement. The migrating radical R′ retains its (right- or left-handed) configuration provided of course that the hydroxyl-bearing carbon is attached to the asymmetric atom of this radical. But the grouping about the carbon atom, to which R′ is migrating, undergoes a Walden inversion (which may be established, of course, only if the starting amino alcohol has been isolated in a stereochemically individual form). All this undoubtedly proves that the intermediate carbonium ion does not appear in the free state: carbonium ions have a planar configuration, and when they figure as intermediate reaction stages, i.e., when the reactions occur by the S_N1 mechanism, there usually takes place complete or far-reaching racemization.

Thus, the stereochemical course of the pinacol-pinacolone rearrangement is the same as in S_N2 reactions. This is, as it were, an S_N2 replacement of the OH or Br groups (of the diazonium group

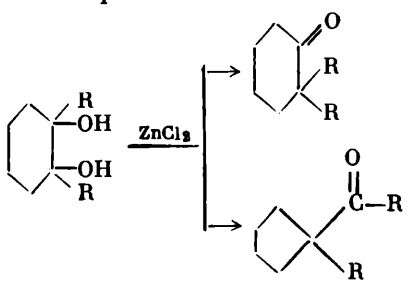
$\overset{+}{N}\equiv N$ in the oxidative deamination) at a carbon atom bearing these groups by the radical R′ from the neighbouring carbon atom.

In the first two cases, the removal of the OH and Br groups is favoured by the action of H^+ or $ZnCl_2$ (a Lewis acid) and Ag^+, and in the third case the rearrangement is encouraged by the spontaneous decomposition of the unstable aliphatic diazonium. The pinacol-pinacolone rearrangement is also aided by the $+T$ effect of the hydroxyl group, which is responsible for the conversion of the alcoholic group of pinacol into the keto group of the pinacolone. It remains to explain formulas IV and IX. They represent the transition state in which R′ has not yet detached from the parent carbon atom but is already in the state of being attached to the carbon receiving the migrating group. Both these carbon atoms and R′ are linked by three-centre electron orbitals. If R′ = H, then we have a hydride shift (page 300). It should however be recalled that, according to the data obtained by Tiffeneau, Orekhov and Bachmann the hydrogen migrates more difficultly than alkyls or aryls.

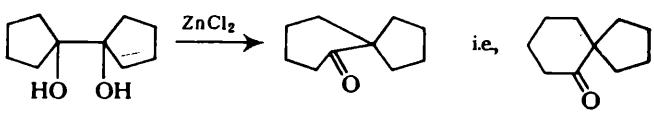
As to the radical R′, the process must be regarded as an electrophilic displacement of the group linked to it:



Pinacol-pinacolone rearrangements have been repeatedly used for altering the structure of alicyclic compounds and for ring expansion or contraction. For example:

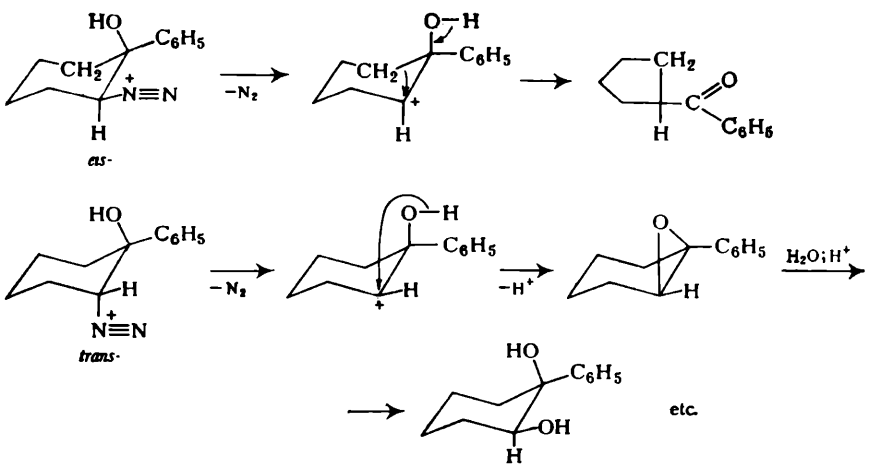


N. D. Zelinsky and N. I. Shuikin have carried out the following synthesis of a spiran ketone:



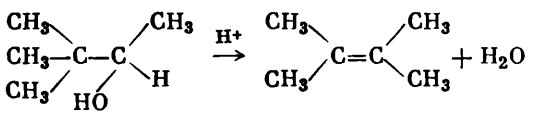
The direction of reactions to the side of formation of a derivative of cyclohexanone or cyclopentyl ketone depends, in particular, on the nature of R and also on the stereochemistry of the ring.

Since the rearrangement occurs with a Walden inversion at the receiving carbon atom, the migrating radical must approach at the opposite side from the leaving group (HO, Br, $\overset{+}{N}\equiv N$ in the examples given above). In the case of the ring-fixed spatial arrangement of these groups relative to the hydroxyl group left, the carbon radical, and the CH_2 group of the ring the geometrical factor shows up and sometimes directs the reaction in different ways. Two examples follow (Curtin):



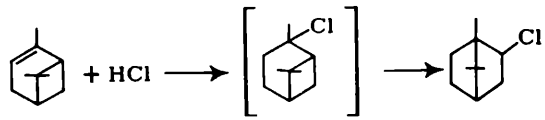
The pinacol-pinacolone rearrangement takes place only for *cis*-amino alcohol (diazotized by nitrous acid): *trans*-amino alcohol retains its skeleton.

The second principal type of rearrangement involving the change of the carbon skeleton is the **retropinacol rearrangement.** In 1901, by dehydrating pinacolone alcohol with acid, N. D. Zelinsky obtained 2,3-dimethyl-2-butene instead of the expected 2,2-dimethyl-3-butene:

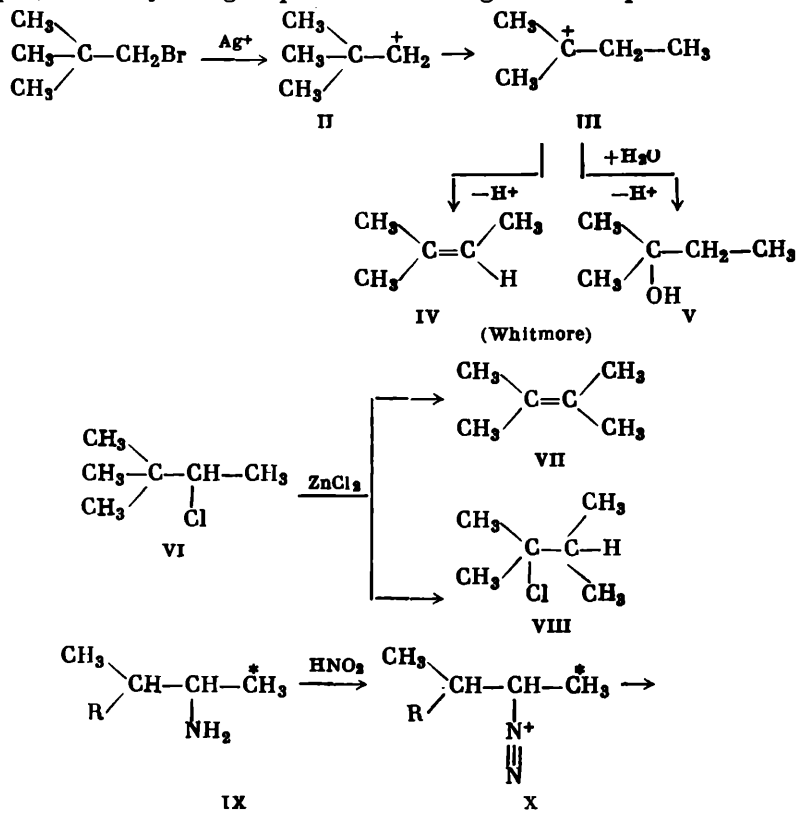


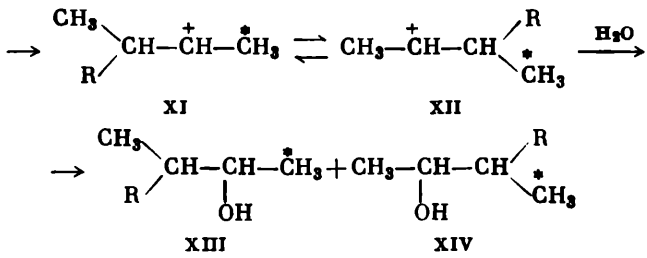
Since here, in contrast to the pinacol-pinacolone rearrangement, the pinacolone skeleton is converted into a symmetrical one, like that of pinacol, this type of rearrangement may be regarded as the retropinacol rearrangement. Such rearrangements have come to bear the

name **Wagner-Meerwein rearrangements** because the first rearrangement of this type that was explained was the rearrangement of pinene to bornyl chloride discovered by E. E. Wagner in 1899:



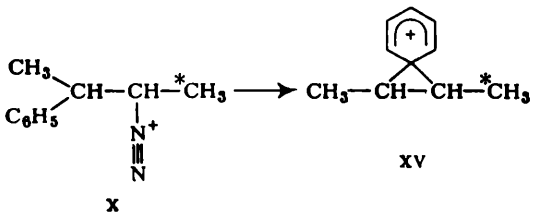
which was later (1910) studied in detail by Meerwein who compared it with the simplest examples of this type of rearrangement. The heterolytic even the ionic character of these rearrangements is evidenced by the fact that they proceed much faster in solvating solvents of high dielectric constant. Just as in the case of the various types of pinacol-pinacolone rearrangements, the group leaving the molecule may be not only the hydroxyl group but also a halogen, the nitrogen of an aliphatic diazonium and an ester group, for example, the tosylate group. The following are examples:





where $\overset{*}{C}$ is the carbon isotope ^{14}C.

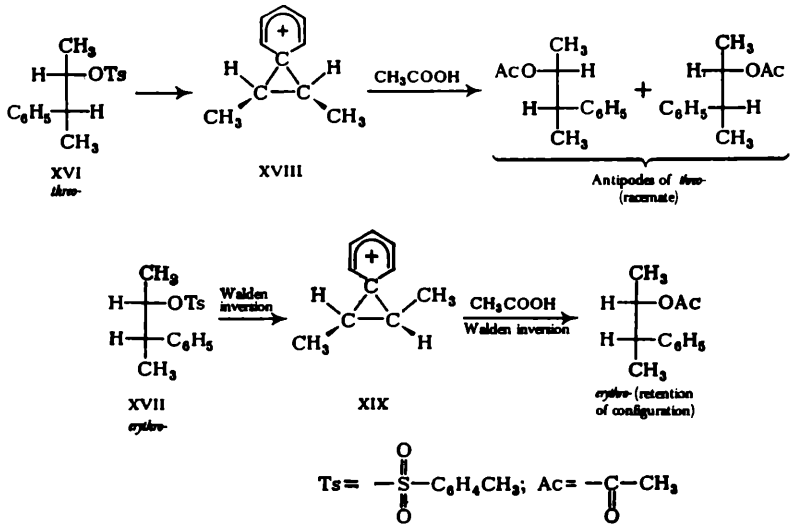
There is no ground for rejecting the involvement of a free carbonium ion in all Wagner-Meerwein rearrangements: the stereochemical course of the reaction is known not in all cases. On the contrary, in many cases equilibria such as XI $\rightleftharpoons$ XII are quite probable. An argument in favour of the participation of a free cation is the fact that in the majority of cases the results of the rearrangements point to the preferred formation of a more stable carbonium ion, i.e., one with a more compensated positive charge. Thus, the more stable of the cations II and III is the latter since its positive charge is suppressed by the $+I$ effect of three alkyl groups, while the charge in the cation II is suppressed by the $+I$ effect of only one *tert*-butyl group. In general, for this reason, carbonium ions with the charge on a tertiary carbon atom are more stable than those with the charge on a secondary carbon atom, and the latter are more stable than carbonium ions of the $-\overset{+}{C}H_2$ type. But if $R = C_6H_5$, it is suggested (Cram, 1949) that formulas XI and XII be replaced by formula XV which represents the intermediate compound—the **phenonium ion**



with the equally probable ring-opening by the action of water and formation of compounds XIII and XIV.

The concept of the phenonium ion was introduced by Cram to account for the stereospecific behaviour of two diastereoisomers of 3-phenyl-2-butyl tosylate in Wagner-Meerwein rearrangements. On acetolysis the *threo*-stereoisomer XVI is completely racemized, and the *erythro*-stereoisomer XVII is converted into the acetate, which retains full optical activity. Cram postulates the formation, as transient forms during the course of the rearrangement, of struc-

tures XVIII and XIX which contain the phenonium ion attached symmetrically to both carbon atoms—the start and the finish carbon atom:

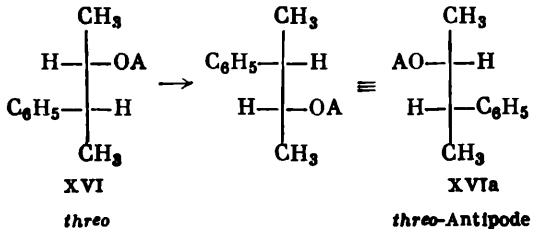


The carbon atom of the aromatic ring, which was originally bound to the start carbon atom, became tetrahedral in the three-membered intermediate form. This means that the plane of the benzene ring became perpendicular to the plane of the drawing. The positive charge on the finish carbon atom is now delocalized over the carbon atoms in the three-carbon ring and, hence, over all the atoms of the benzene ring, which, according to Cram, lowers the energy level of this transient form and thereby accelerates the reaction.

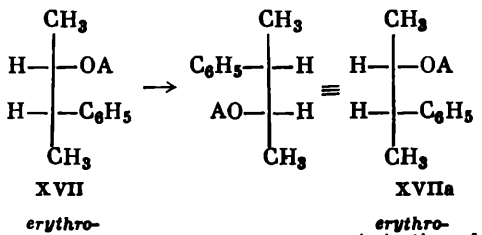
The opening of the hypothetical three-membered cation by the action of acetic acid in the case of *threo*-isomer XVI having a plane of symmetry must lead to the racemate because of the ring-opening being equally probable from both sides, from the left and the right (or, in other words, the two symmetrical molecules involved in the reaction fail to give a single optical form; they yield only the racemate). On the contrary, in the case of *erythro*-isomer XVII the acetolysis of the asymmetrical three-membered structure, regardless of the direction of attack by acetic acid, leads to the original configuration.

It should be emphasized here that both the closure into a three-membered ring with removal of the tosylate anion and the opening of the three-membered ring with reversion of the phenonium ion to a benzenoid form occur with a Walden inversion. Hückel, who debated Cram's interpretation and the very existence of the phenonium

ion and a three-membered ring, pointed out that the stereospecificity of the reaction under consideration may be accounted for by a mere interchange of places between the phenyl group and the tosylate group (or the acetate group which replaces the latter), involving two Walden inversions:



XVI *threo* XVIa *threo*-Antipode



XVII *erythro*- XVIIa *erythro*- (retention of configuration)

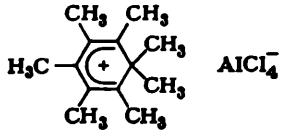
Here OA stands for the leaving tosylate anion or the entering (in Cram experiments) acetate anion.

It goes without saying that under the conditions of the reaction the acetate XVIa may rearrange back to acetate XVI, so that the racemization is caused by two processes XVI $\rightleftarrows$ XVIa.

The objections put forward by Hückel are grounded, and the currently widespread conception of the phenonium ion as an intermediate form in rearrangements cannot be considered completely accepted in science.

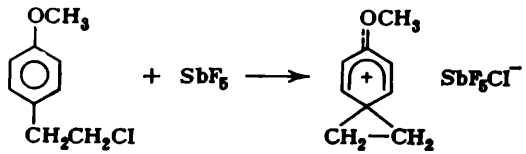
Reactions involving the migration of the aromatic group and not of the alkyl group or hydrogen proceed, in the opinion of the adherents of the phenonium-ion hypothesis, hundreds and thousands of times faster exactly owing to the relatively low energy level of the phenonium ion with its positive carbonium charge delocalized over many atoms. Hückel's objection in this case consists in that structures of the XVIII and XIX types are essentially "classical" and may by no means be regarded as the transition state, and the rate of the reaction is determined only by the energy level of the transition state (page 253). As a matter of fact, stable cations of this kind have already been encountered, for example, in the fol-

lowing form

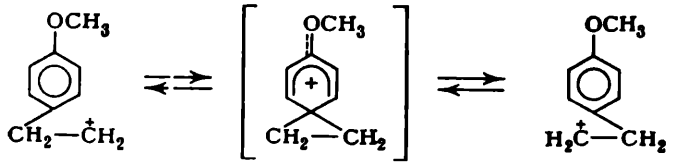


in the description of the Friedel-Crafts reaction (see Volume III, page 41). Thus, structures XVIII and XIX are separated from the reactants and products of the reaction by energy barriers that determine the rate constant of conversions of the starting compound XVI into the intermediate and of the latter into product XVIa and, respectively, of compound XVII into the intermediate and then into product XVIIa. Of course, this may be debated by stating that if both transition states, before and after the intermediate, are close to it in geometry and structure, they are energetically also close to each other. Hence, the energy barriers that separate the intermediate are not high and, consequently, the energy level of this intermediate product nevertheless approximately determines the rate of the reaction (Hammond's postulate).

In 1967, Olah described an experiment that seemed to provide a direct proof of the existence of phenonium ions in certain cases at least. It has turned out that *p*-(β-chloroethyl)-anisole dissolved in excess SbF_5 at —80°C gives a single sharp peak (singlet) in the NMR spectrum in the region of methylene protons. This means that both methylene groups become equivalent after removal of the chloride ion, i.e., after the formation of a carbonium ion:



But if methylene groups were non-equivalent, the NMR spectrum would contain two triplets in this region, belonging to different methylene groups. In actual fact, however, these data do not exclude the rapid reversible isomerization of the "non-classical" carbonium ion, i.e., an equilibrium of the type:

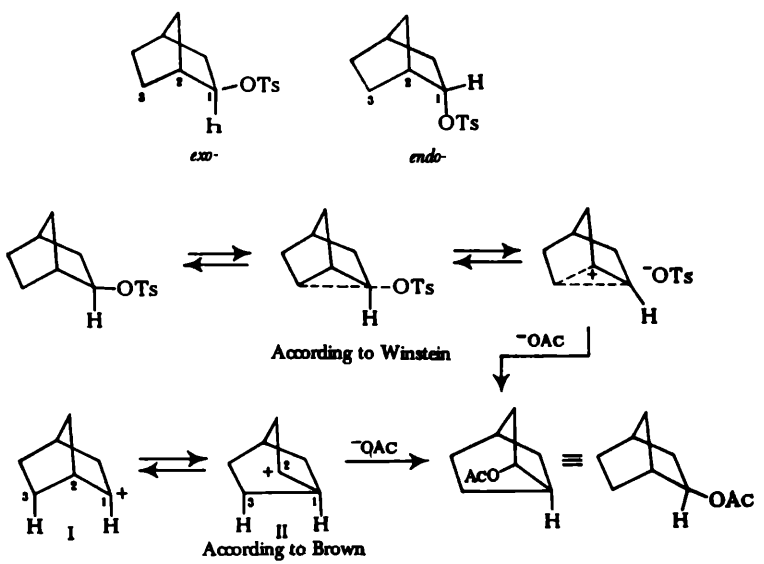


The rate of interconversions of classical carbonium ions must here be too great for nuclear magnetic resonance to detect each carbonium ion as an individual particle.

In some cases, for example, for the Wagner-Meerwein rearrangement, it has been proved that the retropinacol rearrangement proceeds strictly stereospecifically with a Walden inversion at the receiving carbon atom and, besides, at a sharply increased rate. All this undoubtedly supports the concerted mechanism here.

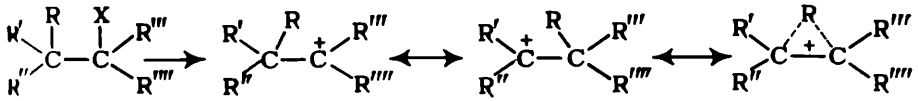
This fact of an enormous increase of the rate of rearrangement in the case of an appropriate configuration (the *exo*-configuration in this particular case) is called **anchimeric assistance** (Winstein) or, what is the same thing, **synartetic acceleration** (Ingold).

There was a dispute in recent years between Winstein and Brown concerning the mechanism of rearrangements with participation of cations of the isobornyl or norbornyl type. As has been established, the acetolysis of the *exo*-isomer of norbornyl tosylate is 1000 times faster than that of the *endo*-isomer and is considerably faster than the same reaction for *tert*-butyl tosylate. According to Winstein, this is accounted for by the fact that steric assistance on the part of the bond being formed is possible only for the *exo*-isomer (in which case the bond being formed and the leaving group will lie in the same straight line, just as in an ordinary nucleophilic substitution reaction). Brown maintains that ordinary classical cations are formed, which are in equilibrium with one another:



According to Winstein, the rearrangement occurs through a nonclassical three-membered cation with its positive charge delocalized

over the three carbon atoms, without formation of a free carbonium ion. The non-classical cation (the concept was first introduced by Winstein) is described by Winstein as a hybrid of resonating structures, which is expressed in a general form by the following scheme:



For the concrete example of isoborneol and camphene it is represented as follows:

A *B* *C*

This interpretation, however, is hardly grounded (Hückel) since electron delocalization may occur inside a definite structure with a fixed position of atomic nuclei. Incidentally, carbon atoms 1 and 3 in structures *A* and *C* are at a distance of 2.5 Å from each other, the distance in structure *B* being 1.5 Å (the length of a single bond).

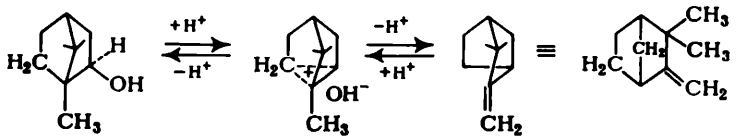
The relatively low rate of acetolysis of the *endo*-isomer is attributed by Brown to steric hindrances (from the hydrogen atom in position 3), which impede the solvolysis, and to the removal of the *endo*-tosylate group.

Brown rejects the role of steric (anchimeric) assistance. His objection is based on his own experimental data showing that the introduction into norbornyl tosylate at position 1 of substituents (CH_3, C_6H_5, p-$CH_3OC_6H_4$), which stabilize the carbonium ion, increases the rate of acetolysis of both the *exo*- (v_{exo}) and the *endo*-isomer (v_{endo}). Further, since the steric assistance must not depend on the presence of a substituent, the ratio of the rates v_{endo}:v_{exo} must have changed appreciably when going from the unsubstituted to the substituted norbornyl tosylate (especially if the stabilizing effect of the substituent on the carbonium ion is comparable with or is greater than the expected anchimeric effect). In reality, however, this ratio remains constant on passing to derivatives containing different substituents including those mentioned above.

Comparing Hückel's theoretical reasoning with Brown's experimental data, we may say that the non-classical cation should be represented more correctly not as an independently existing particle and not as a hybrid of resonating classical cations but as a transition state of the rearrangement, which corresponds not to the minimum but to the maximum of the potential curve (at the top of the barrier

separating the two interconvertible classical cations I and II, page 282).

Let us consider, for example, the rearrangement of isoborneol to camphene and the reverse rearrangement under the action of acids:



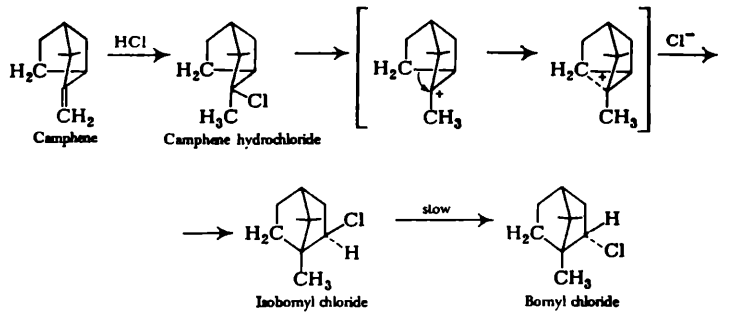
In this case, simultaneously with the separation (on attack of H^+ on OH) of the hydroxyl group the electron pair that bonds the CH_2 group singled out on the scheme begins to detach from the quaternary carbon and to attach itself from the rear to the carbon atom losing the hydroxyl, thereby assisting the removal of the hydroxyl group. Owing to this synartetic acceleration (or anchimeric assistance), the rearrangement of isoborneol and also of isobornyl chloride to camphene takes place thousands of times faster than the rearrangement of the stereoisomeric borneol (or bornyl chloride) to camphene.

At the last stage of the rearrangement the methyl group loses a proton and the electron pair that bounds the proton forms a double bond with the adjacent carbon atom, thereby cancelling the positive charge on the carbonium ion. This ordinary process of stabilization of the carbonium ion by way of its conversion into an olefin has already been considered in the case of the conversion of pinacolone alcohol into symmetrical tetramethylethylene.

The acetolysis of *p*-toluenesulphonates (tosylates) of isoborneol and borneol and, for comparison, that of cyclohexyl-*p*-toluenesulphonate have been studied kinetically. The rate of acetolysis of the latter compound was taken as unity. It has appeared that the rate of acetolysis of isobornyl tosylate is higher by 3.5×10^5, and the rate of acetolysis of bornyl tosylate is higher only by 1.4 times. The synartetic effect was thus observed only in the case of isobornyl tosylate.

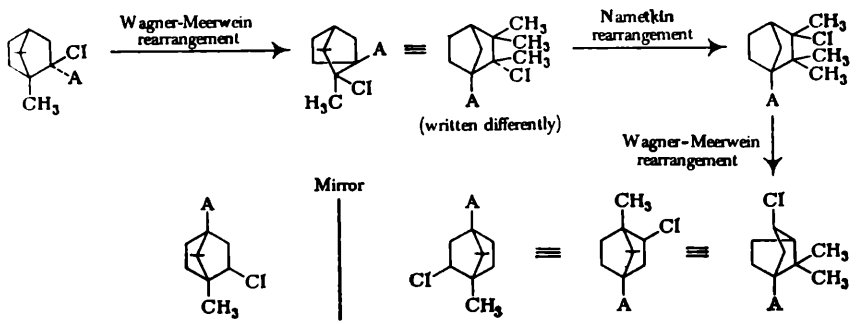
The occurrence of the synartetic process and the conversion of the adduct HCl with pinene, which is a true pinene hydrochloride, into bornyl chloride will be described in Chapter 21. When hydrogen chloride is added to camphene, a very labile camphene hydrochloride is formed, which even when dissolved in dry ethanol at 0°C is converted into isobornyl chloride at a rate 6000 times higher than the rate of alcoholysis of *tert*-butyl chloride under the same conditions. Here again we have the synartetic acceleration of the elimination of the chloride ion at the side of the bonding electrons

of the CH_2 group which migrates to the carbonium ion carbon via the transition state—the non-classical cation:



The formula of the carbonium ion with the fixed charge is given only for the sake of clarity; as a matter of fact, such a carbonium ion has no independent existence and is converted into the transition state with a non-classical three-membered cation, from which the chloride ion is separated synchronously with the migration of the CH_2 group. On attack by the chloride ion the transition state is rapidly converted into isobornyl chloride which stereoisomerizes slowly to bornyl chloride.

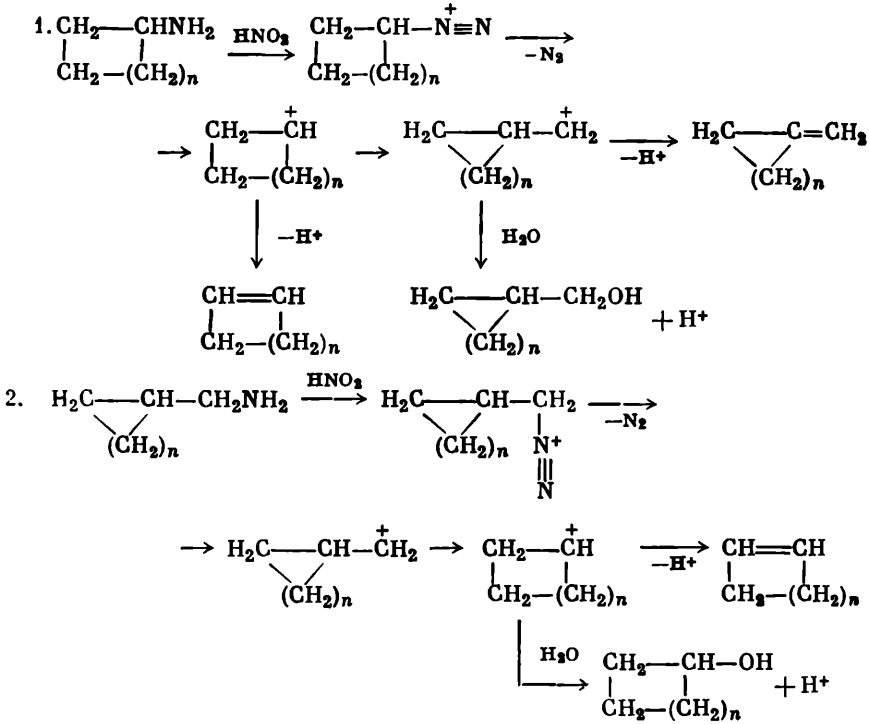
S. S. Nametkin discovered still another type of retropinacol rearrangement in the terpene series, which bears his name. In the **Nametkin rearrangement**, the hydrocarbon radical from the quaternary position and the halogen (or hydroxyl), which are at two neighbouring ring carbon atoms exchange their places. The Nametkin rearrangement is accompanied by the Wagner-Meerwein rearrangement, and, on the whole, the process in the case of the homologue of isobornyl chloride—methylisobornyl chloride—is as follows (A is methyl in this case):



If A is hydrogen and not a hydrocarbon radical, the Nametkin rearrangement brings about the conversion of *D*-isobornyl chloride

into L-isobornyl chloride (and the reverse conversion), i.e., results in racemization. If A is a hydrocarbon radical, isomerization takes place.

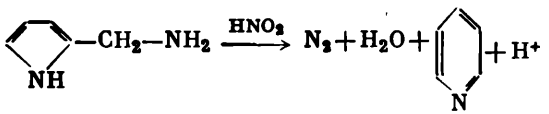
The isomerization of rings under the action of nitrous acid on alicyclic amines, which were discovered and studied by N. Ya. Demyanov and which are called **Demyanov rearrangements**, also belong to the category of retropinacol rearrangements. The general scheme of these rearrangements may be formulated as follows:



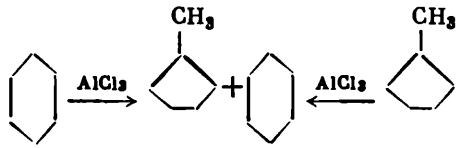
Not all the ring-contractions and -expansions involved in these rearrangements proceed equally easily. The five-membered ring is readily expanded into a six-membered ring, and the seven-membered ring contracts to a six-membered ring, which predominantly remains unaltered. As regards the interconversion of three- and four-membered rings, it does occur but the mechanism of such interconversions is probably not so simple.

Along with the rearrangement products, there are also formed alcohols—the products of the normal substitution reaction in which the NH_2 group is replaced by a OH group.

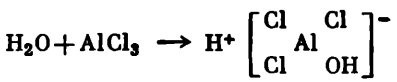
As has been shown by N. I. Putokhin, the Demyanov rearrangements are applicable to the heterocyclic series, for example:



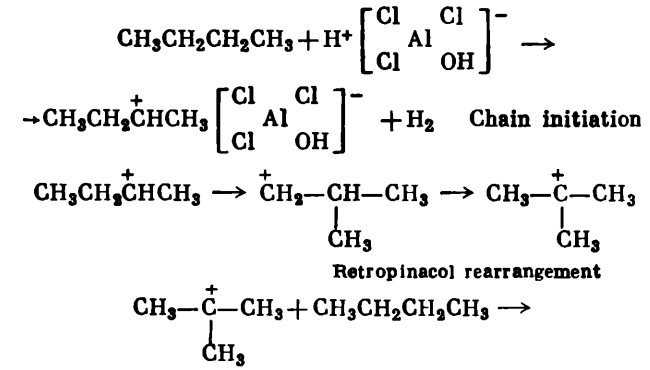
N. D. Zelinsky and his school have discovered numerous rearrangements of aliphatic and, in particular, alicyclic hydrocarbons under the influence of aluminium chloride. For instance, starting with cyclohexane or with methylcyclopentane one can obtain an equilibrium mixture:

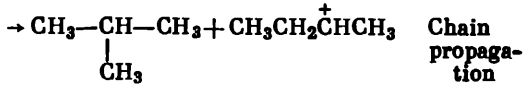


A number of such reactions in the aliphatic series were also discovered by Nenitzescu and co-workers, who regarded them as retropinacol rearrangements proceeding by an ionic-chain mechanism. Aluminium chloride must contain a small amount of moisture, in the presence of which a complex acid is formed:

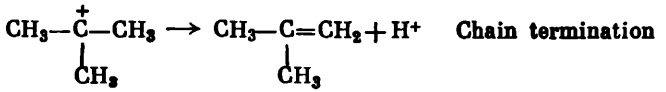


This complex acid acts on a hydrocarbon, detaching (predominantly from the secondary or tertiary position) a hydride ion and liberating molecular hydrogen. The carbonium ion formed undergoes a retropinacol rearrangement to the isomeric carbonium ion, which detaches a hydride ion from the new hydrocarbon molecule, converting it into a carbonium ion and so on until the ionic chain is terminated by the expulsion of a proton with the formation of an olefin:

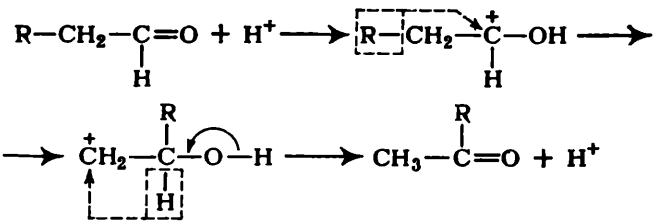




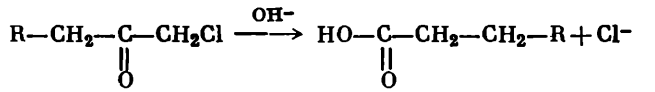
etc.



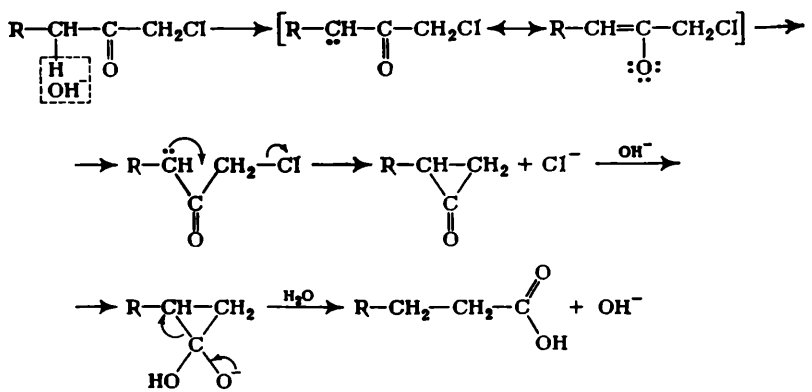
Also related to retropinacol rearrangements are the rearrangements discovered by S. N. Danilov and E. D. Venus-Danilova, which are the conversions of aldehydes into ketones by the action of concentrated sulphuric acid:



Favorsky rearrangement involves the conversion of α-chlorosubstituted ketones into acids under the influence of alkalis:

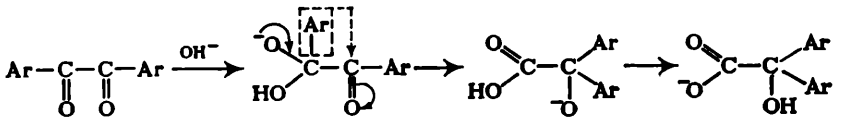


This rearrangement may be regarded formally as a retropinacol rearrangement proceeding with the migration of the RCH_2 grouping to the site that was occupied by chlorine, but the reaction conditions are quite different: the chloride ion is not attacked, and the reaction involves the action of alkali which can remove an α-proton. It is therefore considered to be a different type of rearrangement, in which the driving force is the formation of a carbonium ion:

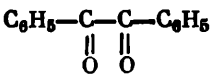


Thus, the Favorsky rearrangement proceeds through the formation of a derivative of cyclopropanone, which is unstable in alkaline medium. It is a nucleophilic substitution reaction with respect to the CH_2Cl group.

The **benzilic acid rearrangement** which is important for the aromatic series (it is rarely effected in the aliphatic series) involves the action of alkali on α-diketones:

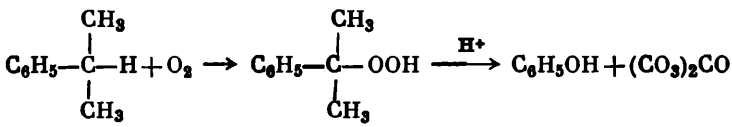


The acid $(C_6H_5)_2C(OH)COOH$ is known as benzilic acid, and the diketone

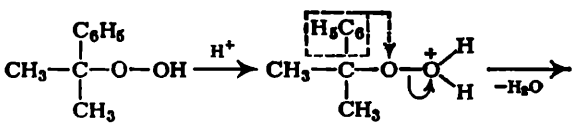


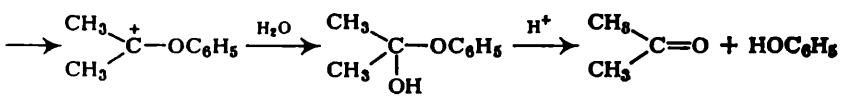
is called benzil (compare its mechanism with that of the pinacol rearrangement).

The industrial method of preparing phenol and acetone by the reaction (see Volume III, page 129)



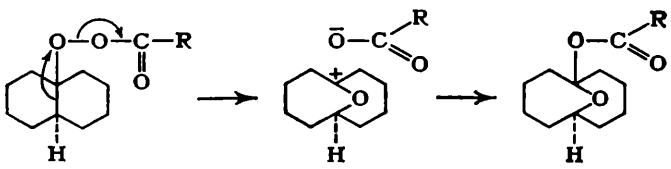
is also based on the rearrangement of the carbon skeleton, which is expressed by the scheme:





A similar course is followed by the **Criegee rearrangement**, an example of which is the conversion of the ester of decalin-9-hydro-

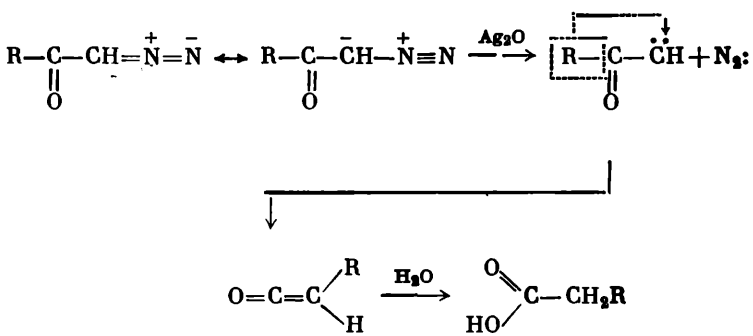
peroxide into the ester of 1-hydroxy-1,6-epoxycyclodecane:



This rearrangement takes place on heating in an ionizing solvent and is employed for opening carbocyclic compounds.

20.2. Rearrangements Involving Carbenes and Carbenoids as Intermediates

Wolff-Arndt Rearrangement. Under the catalytic action of solid silver oxide, α-diazo ketones rearrange to ketenes, and on further treatment with water there are formed acids with the same number of carbon atoms as there were in the starting ketones:

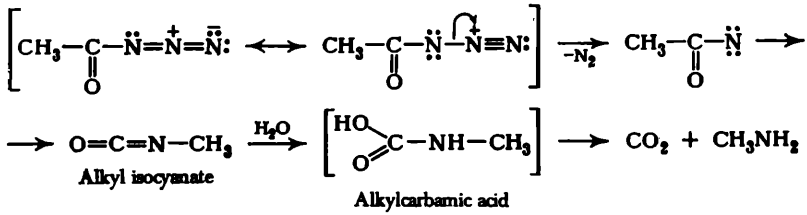


The fundamental difference between this rearrangement and all the previous ones is that the migration occurs not to a carbonium ion but to a neutral carbon atom with an incomplete electron shell (with a sextet of electrons)—carbene.

There is a series of analogous rearrangements in which the nitrogen atom is the atom with an unfilled electron shell (also a sextet), which accepts the migrating group.

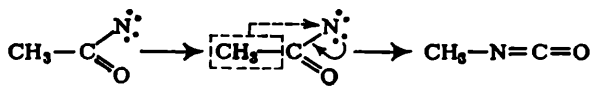
Rearrangements with transfer of the migrating group to nitrogen. Most closely related to the Wolff-Arndt rearrangement is the **Curtius rearrangement**, which occurs on heating acid azides (see Volu-

me I, page 234):



The intermediate unstable compound formed immediately after the elimination of a nitrogen molecule contains a nitrogen atom with a sextet of electrons, i.e., with an unfilled (vacant) orbital. Atoms such as we have seen above are electrophilic like cations, although they are formally neutral. They are close in this respect to the carbon atom in carbenes

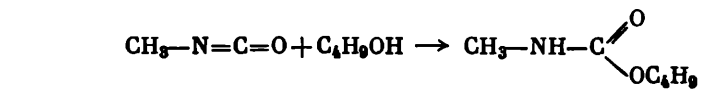
and may be called **carbenoid atoms** (D. N. Kursanov and M. E. Volpin). Further, the alkyl group in this intermediate compound migrates to nitrogen together with a pair of bonding electrons and these electrons fill the vacant orbital of the nitrogen. No negative charge appears on the nitrogen atom since the free electron pair of nitrogen simultaneously becomes a π-pair forming a bond with carbon, as a result of which a molecule of alkyl isocyanate (the ester of isocyanic acid) is formed:



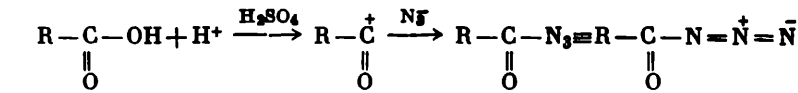
The removal of the nitrogen molecule from the azide may also occur simultaneously or almost simultaneously with the starting rearrangement, so that the "carbenoid molecule" does not exist in the free state even for an instant.

The situation is analogous in the Schmidt, Lossen and Hofmann rearrangements which are described more briefly below. The product of all these rearrangements is an alkyl isocyanate which is instantly hydrolysed in aqueous medium; the alkylcarbamic acid formed does not exist in the free state (just as carbonic acid) and decomposes into carbon dioxide and an amine. But if the decomposition of azides is conducted not in water but in an alcohol, there will be formed the products of addition of the alcohol to the alkyl isocya-

nate, i.e., urethanes which are quite stable:

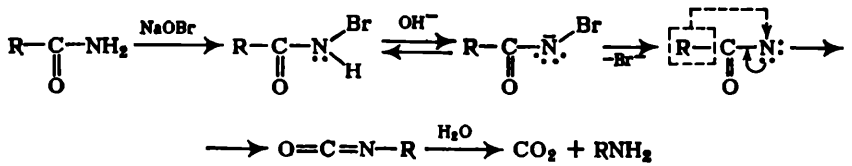


The **Schmidt rearrangement** involves the direct conversion of acids into amines with a chain containing one carbon atom less. A solution of a carboxylic acid in concentrated sulphuric acid is reacted with sodium azide. Under such conditions most carboxylic acids give reversibly **acylium ions** which form acid azides with the azide anion:



The reaction then progresses in the manner described above for the Curtius rearrangement. Synthetically this reaction has an advantage over the Curtius or Hofmann rearrangement, which consists in that the stages of formation of an azide or an amide from the acid are avoided (of course, it is advantageous only when the total yields do not differ essentially).

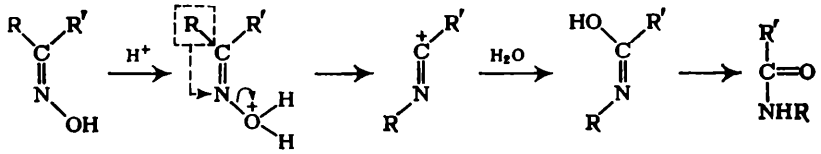
The familiar **Hofmann rearrangement** which starts from the amides of carboxylic acids proceeds in aqueous medium and affords the same products that are obtained by the Schmidt or Curtius reaction in aqueous medium. The action of an alkaline solution of bromine leads largely to a N-bromosubstituted amide which is unstable under these conditions. Further, the hydroxyl of alkali removes a proton and the anion formed dissociates with elimination of the bromide ion. This results in the formation of the same intermediate compound as in the previous rearrangements. It is possible that the dissociation with elimination of the bromide ion occurs simultaneously with the rearrangement:



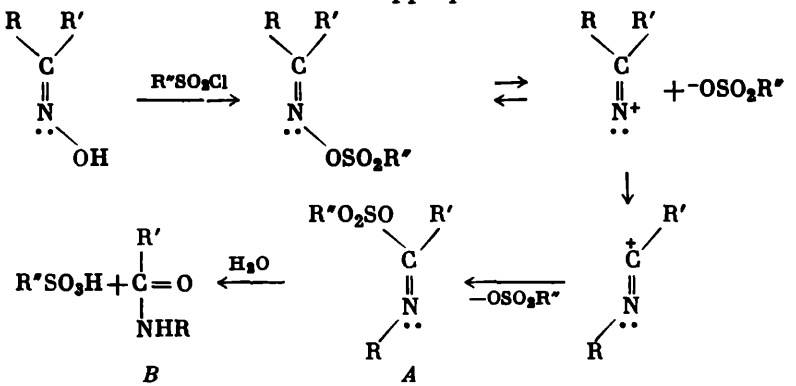
According to Wallace, in the Curtius, Hofmann, Lossen, and Wolff rearrangements the migrating group retains its configuration.

The **Beckmann rearrangement** takes place by the action of Lewis acids, PCl_3, PCl_5, and also of the acid chlorides of sulphonic acids and concentrated mineral acids, such as sulphuric acid, on ketox-

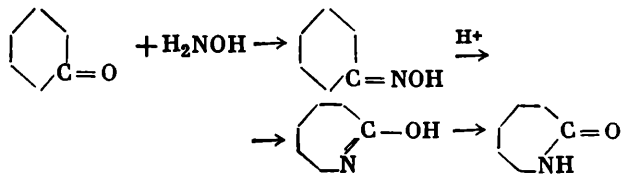
imes. This rearrangement leads to acid amides by the following route:



If the rearrangement occurs under the action of acid chlorides of sulphonic acids, first hydrogen chloride is eliminated and the acid residue takes the place of the hydroxyl hydrogen; such compounds can in a number of cases be easily isolated. Further, in a polar solvent, especially on heating, they dissociate (the heterolysis of the N—O bond), so that the nitrogen atom is left with its electron shell unfilled. The electron pair of the C—R bond is trapped into this vacant shell, the radical migrates and the cation formed becomes attached to the appropriate anion:

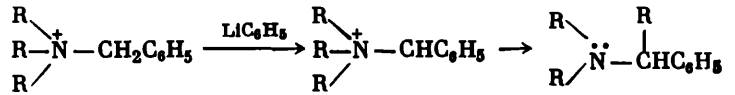


The rearrangement product of the type *A* can be isolated. It is easily hydrolysed to acid amide *B*. If the reaction is conducted in aqueous medium, the water adds on to the cation and the amide is directly produced. As has been strictly proved by many investigators (see Volume II, page 166), this rearrangement is completely stereospecific: the radical migrates that is in the *anti*-position to the leaving hydroxyl. The Beckmann rearrangement is used, for example, for opening a carbocyclic compound and for preparing caprolactam (in the production of nylon 6):



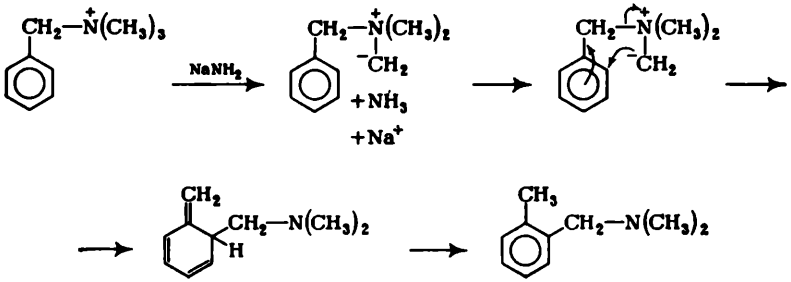
All the rearrangements considered above are known as **nucleophilic or sextet rearrangements.** The first name implies that the radical migrates to the electron-deficient centre. For the majority of these rearrangements it has been proved that it is the more powerful electron-donating radical that migrate in the first place and at a greater velocity (and aryls do so more rapidly than alkyls).

Stevens rearrangement. Quaternary ammonium salts which have a sufficiently mobile α-hydrogen atom (in groupings, such as $-CH_2C_6H_5$, $-CH_2C(=O)-R$) lose this hydrogen in the form of a proton under the action of strong bases (NaOH, LiC_6H_5), this resulting in the formation of an ylide which then undergoes an electrophilic rearrangement



that is, in this case the migrating radical, leaving a pair of bonding electrons on the nitrogen atom, shifts to the negatively charged carbon.

The **Sommelet rearrangement** takes place only in those cases when R=alkyls in the above scheme. It takes the following course:



20.3. Rearrangements Involving the Migration of π-Bonds

Allylic Rearrangements. When an allyl halide and its derivatives are subjected to nucleophilic attack, the products of isomerization are obtained along with the normal substitution product: the nucleophilic reagent takes the place not of the halogen being replaced but of carbon 3, and the double bond is shifted. For an allyl halide

labelled at carbon (^{14}C) this is formulated as follows:

$$*CH_2=CH-CH_2-Cl \xrightarrow{OH^-} \begin{cases} \longrightarrow HO-CH_2-CH=\overset{*}{C}H_2 \\ \longrightarrow CH_2=CH-\overset{*}{C}H_2OH \end{cases} + Cl^-$$

Since the allyl halide when present in media of high dielectric constant reacts with nucleophiles by the S_N1 mechanism, the reaction must proceed with the preliminary dissociation into ions. Even before the wide application of the concept of mesomerism in organic chemistry (in the thirties of this century) Prévost and Kirrmann advanced a theory, which they called **synionism**, to account for such a dual reactivity, i.e., a theory of the unified structure of the allylic ion in this case, which is formulated in modern language as follows:

$$CH_2=CH-\overset{*}{\overset{+}{C}}H_2 \quad \text{or} \quad CH_2=CH-\overset{*}{\overset{+}{C}}H_2 \longleftrightarrow \overset{+}{C}H_2-CH=\overset{*}{C}H_2$$

$$RCH=CH-\overset{+}{C}H_2 \quad \text{or} \quad RCH=CH-\overset{+}{C}H_2 \longleftrightarrow R\overset{+}{C}H-CH=CH_2$$

In this case, the chlorine atom split off as the anion may recombine with a carbonium ion at either of the two carbon atoms bearing a partial positive charge, with the formation of

$$RCH=CH-CH_2Cl \quad \text{or} \quad RCHCl-CH=CH_2$$

This is the case of **allylic anionotropy**, and the phenomenon is righteously regarded as the **anionotropic tautomerism**:

$$RCH=CH-CH_2Cl \rightleftarrows \underset{\displaystyle Cl}{RCH-CH=CH_2}$$

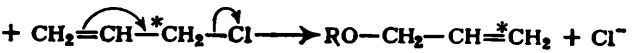
In the above-written reaction with the carbon isotope, the structure of the carbonium ion is fully symmetrical and the charge is distributed uniformly between the terminal carbon atoms. Therefore, the occurrence of the reaction without rearrangement and with allylic rearrangement is equally probable. In the second case, this is not so, of course: the carbonium ion with the cationic centre at the secondary carbon atom is more stable than that at the primary carbon, and the substitution at the secondary carbon atom must predominate.

The enhanced ability of an allyl halide (as compared with saturated halides) to undergo electrolytic dissociation is accounted for by the stability of its cation—because of the charge distribution between two carbon atoms the energy of such a carbonium ion decreases.

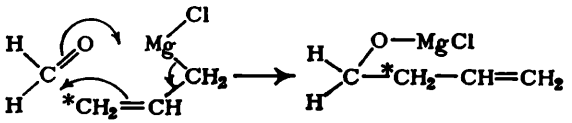
Allylic rearrangements, however, occur also in substitution reactions taking place by the S_N2 and S_E2 mechanisms, i.e., without

electrolytic dissociation. This is a typical case of reactions with transfer of the reaction centre via a system of conjugated bonds, in this case, of σ,π-conjugated bonds (see Volume I, page 393). We shall describe the course of such reactions by making use of the symbolism of the English school.

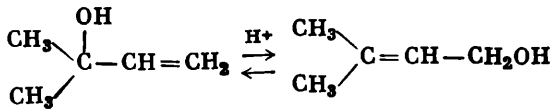
1. The anionotropic allylic rearrangement (in a medium of low dielectric constant, the S_N2 mechanism):



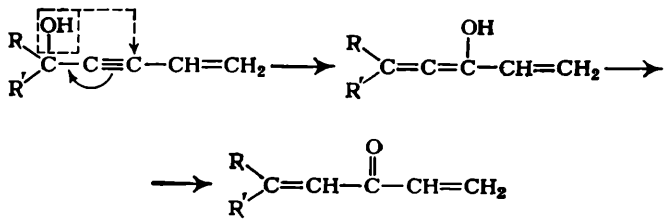
2. The cationotropic allylic rearrangement:



One of the important simplest cases of **anionotropic allylic rearrangement** is the reversible rearrangement of dimethylvinylcarbinol to isobutenylcarbinol (A. E. Favorsky, A. I. Lebedeva):



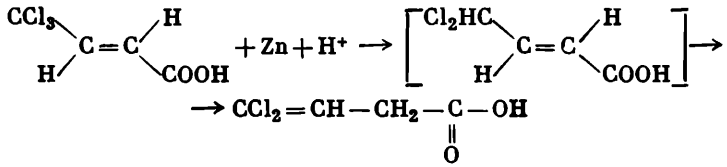
As a matter of fact, the conversion of vinylethynylcarbinols into divinyl ketones (under the action of the mercuric ion) discovered by I. N. Nazarov may also be classed as a rearrangement of this type:



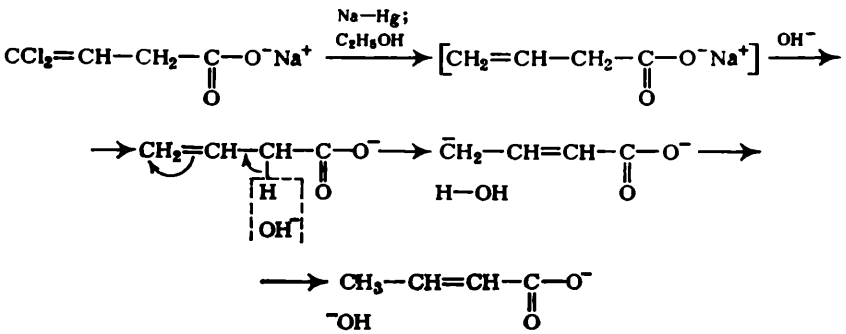
Such a synthesis of divinyl ketones from vinylethynylcarbinols (which are prepared by the action of vinylacetylene on ketones $\begin{matrix} R \\ \diagdown \\ R' \end{matrix}\!\!>\!C=O$ in the presence of KOH) enabled Nazarov to make wide use of divinyl ketones in the synthesis of cyclic systems.

The simplest examples of **cationotropic allylic rearrangements** are prototropic allylic rearrangements, for example, the rearrangement

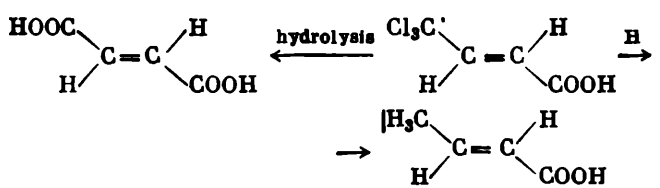
of γ,γ,γ-trichlorocrotonic acid by the action of zinc and acetic acid. Possibly, as a result of the replacement of chlorine by hydrogen, there is first formed dichlorocrotonic acid which, as has been proved by A. N. Nesmeyanov, R. Kh. Freidlina, and L. I. Zakharkin, rearranges to dichlorovinylacetic acid:



The subsequent reduction of dichlorovinylacetic acid occurs only under the influence of sodium amalgam in alcohol. This involves the reverse allylic rearrangement and leads to crotonic acid:



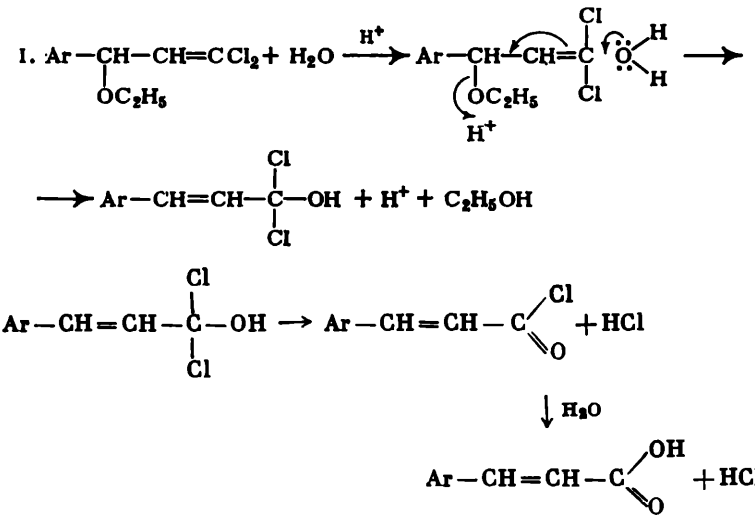
Thus, two prototropic allylic rearrangements (one in acid and the other in alkaline medium) are involved in the conversion of trichlorocrotonic acid into crotonic acid by a two-stage reduction. The reaction proceeds without change of configuration only because the *trans*-isomers are more stable both for the starting and for the end acid. Otherwise, the configuration would not be retained since stereoisomerism disappears at the stage of dichlorovinylacetic acid. Incidentally, Auwers and, later, many other scientists erroneously believed that the agreement discovered by this author is a proof of the *trans*-configuration of crotonic acid:



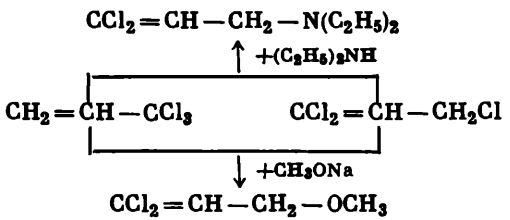
(Auwers' incorrect argument)

This is correct in itself but is not confirmed by the above conversions because of the allylic rearrangement.

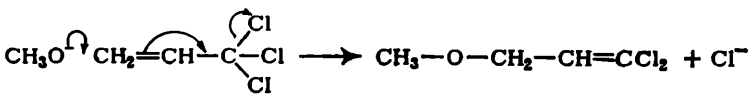
We shall cite several examples of more complicated allylic rearrangements which proceed with transfer of the reaction centre by the S_N2 mechanism (Freidlina, Zakharkin and co-workers):



II. The action of a number of nucleophilic reagents on the isomers $CH_2=CH-CCl_3$ and $CCl_2=CH-CH_2Cl$ gives in both cases the products of replacement of one chlorine atom by a nucleophile. The reaction of the first isomer involves an allylic rearrangement, while that of the second does not:



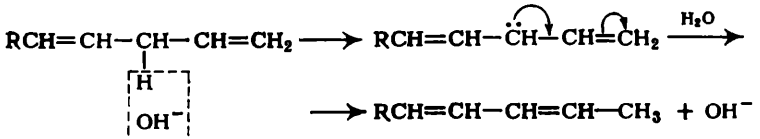
In the first case, the nucleophile evidently attacks the terminal CH_2 group, for example:



The heterogeneous catalysis over basic catalysts (e.g., Al_2O_3) or in the presence of bases involves the shifts of the double bonds and

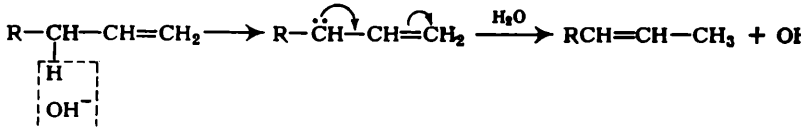
protons, which occur by the mechanism of the **prototropic allylic rearrangement.** Some examples are given below.

1. Double bonds, if there are two or more of them, tend to shift into the conjugated position which is energetically more stable:

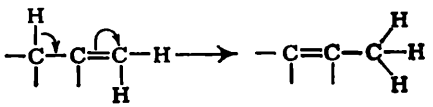


If the double bond is contained in a side chain of an aromatic compound, it also migrates to the position conjugated with the aromatic nucleus.

2. The double bonds at the end of the molecule tend to migrate closer to the centre:



No less important than the migration of multiple bonds in rearrangements of this type is the shift of the proton that converts a methylene group into a methyl group. Hence, the meaning of the reaction may be expressed by the following scheme:



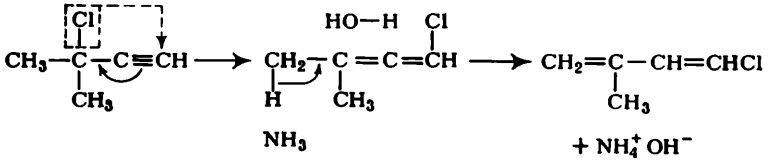
regardless of the fact whether the proton shifts to a new place within the molecule or is first detached by the base and then transferred to a new place by the solvent or a conjugated acid. From the last scheme it is seen that we have here a prototropic allylic rearrangement.

Migration of Triple Bonds. We have already considered the acetylene-allene-diene rearrangement discovered by Favorsky (see Volume I, page 359) which takes place under the action of strong bases; it is formulated as follows:

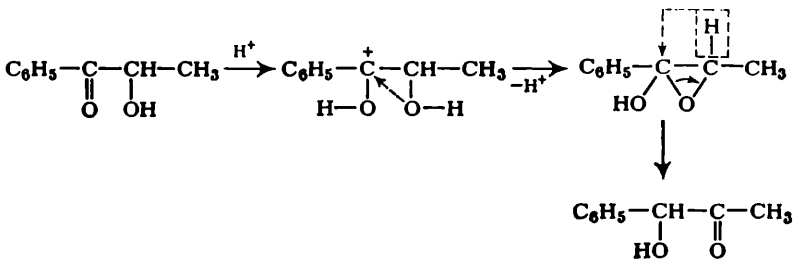
$$RCH_2-CH_2-C\equiv CH \longrightarrow RCH_2-CH=C=CH_2 \longrightarrow RCH=CH-CH=CH_2$$

This rearrangement evidently proceeds as a prototropic (i.e., cationotropic) rearrangement, just as the above-described double-bond migrations.

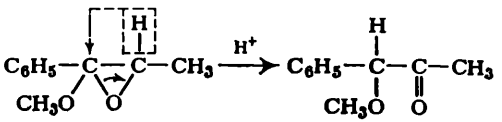
T. A. Favorskaya has discovered the acetylene-allene-diene rearrangements of the halogen-substituted homologues of acetylene, which occur under the influence of the ammine of cuprous chloride in ammonium chloride and are, possibly, a sequence of one anionotropic (acetylene → allene) and one prototropic (allene → diene) rearrangements:



Acyloin Rearrangements. A. E. Favorsky discovered the interconversion of unsymmetrical α-ketols. For example, methylbenzoylcarbinol when reacted with acid rearranges to phenylacetylcarbinol. T. I. Temnikova, who extensively studied rearrangements of this type, suggested a plausible explanation for their occurrence with the participation of the neighbouring group (cf. Volume I, page 213):



Temnikova has shown that in ethers of α-lactols—the model compounds of the expected intermediates of the rearrangement—there actually takes place the rearrangement of the oxide ring to a keto group:

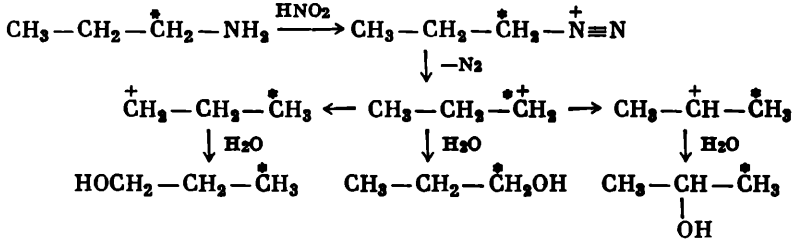


20.4. Hydride Shifts

The above-described transfers of multiple bonds in the molecule may, in principle, be regarded as proton shifts: the proton from the allylic position migrates to a CH_2 group, converting it into CH_3.

This is accompanied by the conversion of the electron pair of a carbon-hydrogen bond into a π-pair and the reverse conversion of the π-pair into a pair that binds the proton (from the solvent).

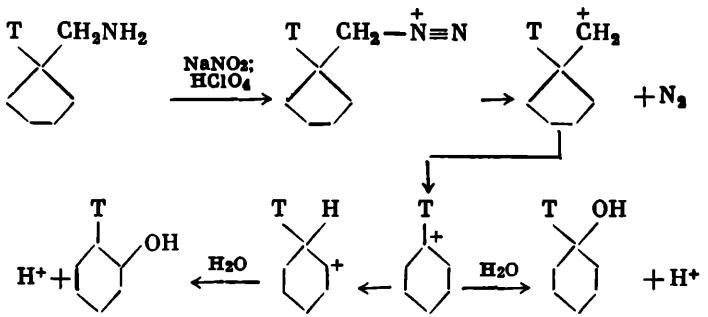
Rather often there are observed shifts of a hydrogen atom together with its pair of bonding electrons (**intramolecular hydride shifts**). They are quite similar to the retropinacol rearrangement, in which a radical migrates also with its pair of bonding electrons. It should be kept in mind, however, that by the ease of migration of radicals (and atoms) in this rearrangement (page 273) hydrogen occupies the last place. And nevertheless hydride shift sometimes prevails. As an example, we shall cite the action of nitrous acid on *n*-propylamine labelled by ^{14}C at the carbon atom carrying an amino group. O. A. Reutov has established that the reaction proceeds as follows:



Thus, the hydroxyl group in the resulting propyl alcohol (primary and secondary) has been found to be situated at any of the three carbon atoms.

Naturally, hydride shifts also complicate other reactions, the intermediate stage of which is the formation of a carbonium ion, say, the Demyanov rearrangement.

Having labelled molecules of alicyclic amines with tritium (T), Reutov and Yu. G. Bundel observed the following hydride transfers that accompanied the Demyanov rearrangement:



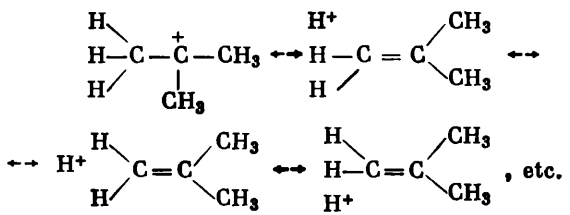
As a result of the subsequent hydride shifts, the carbonium ion centre is also transferred into positions 3 and 4 of the cyclohexane ring.

More extensively studied are **intermolecular hydride shifts** in which the carbonium ion pulls out a hydride ion from another molecule (of the same kind or a different one), converting it into a carbonium ion. Such processes may proceed as chain ionic reactions. Hydride shifts of this kind have been intensively studied, for example, by D. N. Kursanov, V. N. Setkina, Z. N. Parnes and co-workers.

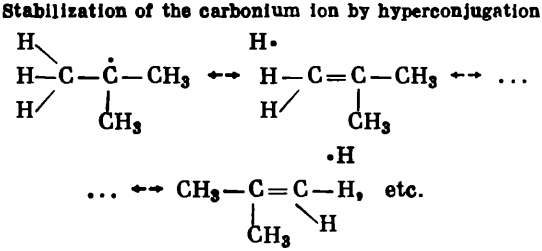
20.5. Homolytic Rearrangements

Rearrangements of free radicals (proceeding, of course, homolytically) became known in the period 1940-1950 and were studied less than heterolytic rearrangements.

Radicals with an unpaired electron at a tertiary carbon atom are the most stable and those with an unpaired electron at a primary carbon atom the least stable. Therefore, at a temperature equal to or higher than 250°C the primary radicals isomerize to secondary (or tertiary) ones, and this reaction requires a small amount of activation energy (about 9 kcal/mole). Perhaps, such a stabilization of an odd electron at a tertiary (and a secondary) carbon takes place in an analogous manner to the stabilization of the carbonium ion, which may be expressed in terms of resonance theory as follows:



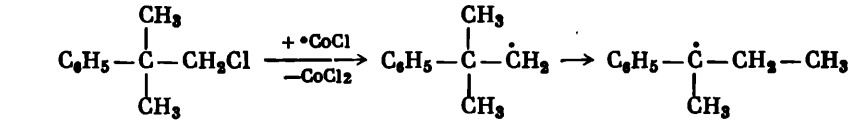
Stabilization of the carbonium ion by hyperconjugation



Stabilization of the free-radical centre

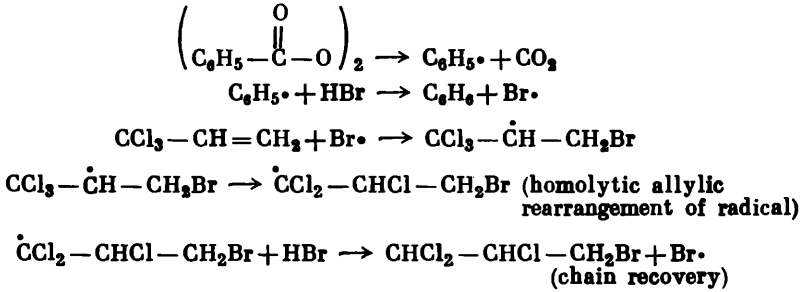
Homolytic rearrangements proceeding in the liquid phase became known later. The first rearrangement of this kind was probably the one discovered by Kharasch in 1944. It is the rearrangement of the so-called neophyl (2-phenyl-2,2-dimethylethyl) radical to

a tertiary radical:



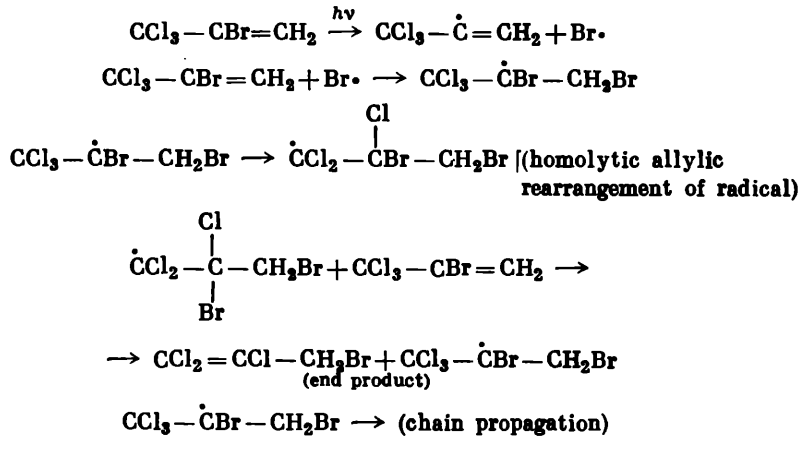
Freidlina and co-workers (1950-1965) discovered and studied systematically the homolytic rearrangements of purely aliphatic unsaturated halogen-substituted compounds, which are rearrangements of the allylic type. The rearrangement always occurs to the side of formation of a more stable radical, in this case a radical whose carbon atom carries more halogens.

Hydrogen bromide in the presence of benzoyl peroxide adds to 1,1,1-trichloropropene with a homolytic allylic isomerization:



Another example is the isomerization of $CCl_3-CBr=CH_2$ to $CCl_2=CCl-CH_2Br$ under the influence of light or a peroxide, i.e., if the homolytic chain reaction is initiated by addition of free radicals.

This homolytic isomerization is believed to proceed by the following scheme:



An evidence for the homolytic chain mechanism of the reaction is its initiation by substances which are free-radical generators, and its termination by inhibitors of chain radical reactions, such as hydroquinone.

It is interesting to note that the homolytic allylic rearrangement of $CCl_3—CBr=CH_2$ (I) leads to a product entirely different from the one obtained by the anionotropic rearrangement (II) of the same compound:

I. $CCl_3—CBr=CH_2 \xrightarrow{h\nu} CCl_2=CCl—CH_2Br$ (chain homolytic rearrangement)

II. $CCl_3—CBr=CH_2 \xrightarrow{SbCl_5} CCl_2=CBr—CH_2Cl$ (anionotropic rearrangement; A. Nesmeyanov, Freidlina, Kost)

Chapter 21

Isoprenoids

21.1. Terpenes and Terpenoids

Widely distributed in the plant kingdom are compounds having an open-chain and isocyclic structure, which may formally be regarded as dimers (terpenes), trimers (sesquiterpenes) or polymers (polyterpenes) of isoprene and their oxygenated derivatives (terpenoids). While studying isoprene, we encountered a terpene—racemic limonene (dipentene) and polyterpenes—natural rubber and guttapercha. The monoterpenes $C_{10}H_{16}$ have the doubled molecular formula of isoprene and, hence, in case they belong to the aliphatic series they must have three double bonds; if there is one alicyclic ring, two double bonds must be present, and, finally, bicyclic terpenes must have one double bond. Thus, according to the chemical classification, even monoterpenes belong to different classes of hydrocarbons and are classified into a separate group contrary to the chemical classification, by the phytochemical criterion. This may however be justified by the fact that there are many reactions that correlate the aliphatic, cyclic and bicyclic terpenes by involving their interconversions. Although some terpenes can (as we have seen in the case of limonene and natural rubber) be prepared from isoprene, there is no isoprene in the plants, and the path of biosynthesis of terpenes and terpenoids is different.

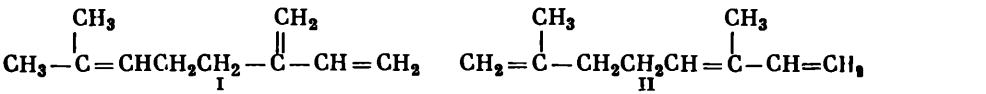
When incisions are made in the bark of the conifers, turpentine resin exudes in considerable quantities from the tree. The resin is collected chiefly from the various species of pines. By distillation in steam the resin is separated into volatile **turpentine oil** and non-volatile **rosin**, or **colophony** (see below). Oil of turpentine is a mixture of various monoterpenes $C_{10}H_{16}$, whose composition depends on the species of the pine and the locality. It is used in the synthesis of camphor, in medicine and in the synthesis of drugs such as terpin hydrate, and certain fragrant compounds, say, terpineol. Turpentine oil is employed also as a solvent and diluent for oil paints.

On steam distillation of flower petals* or leaves of some plants the top layer of the distillate is collected, which is the essential oil of a given flower. It consists mainly of terpenoids, i.e., oxygenated derivatives of terpenes.

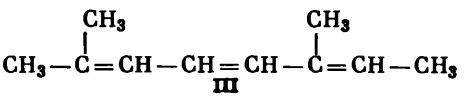
Essential oils find application in perfumery as such or individual components are isolated from them, say, geraniol, citronellal, etc.

A. Monoterpenes and Terpenoids

Acyclic Terpenes and Terpenoids. There are known two main aliphatic terpenes contained in essential oils (for example, hop)—**myrcene** I and **ocimene** II:

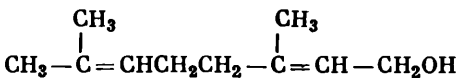


By strongly heating the bicyclic terpene α-pinene (see page 314) B. A. Arbuzov isomerized it to **alloöcimene** III

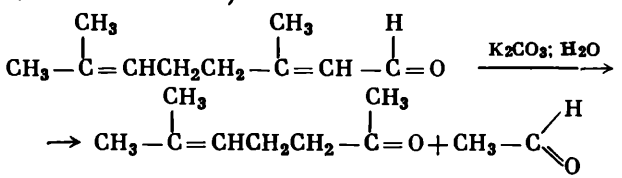


The structure of each of these hydrocarbons is easily established by ozonolysis.

The essential geranium oil (and a number of other essential oils) contains the alcohol **geraniol**



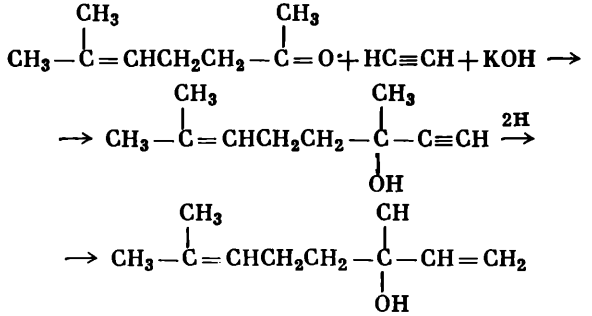
which finds application in perfumery. The cautious oxidation of geraniol (for example, by the Oppenauer method) gives the corresponding aldehyde (with the odour of lemon), **citral**. The structure of this aldehyde follows from its decomposition on boiling with K_2CO_3 into 6-methyl-5-hepten-2-one and acetaldehyde (the inversion of croton condensation):



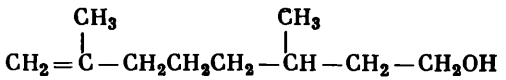
By reacting methylheptenone with acetylene and KOH and subjecting the triple bond to partial hydrogenation Ruzicka produced

* Use is also made of the "enfleurage" method: flower petals are placed in a special chamber between two plates covered with tallow or vaseline which absorbs the perfume to give a pomade from which the perfume is subsequently extracted by a solvent.

the racemic **linalool**, an isomer of geraniol, which is found in oil of lavender:

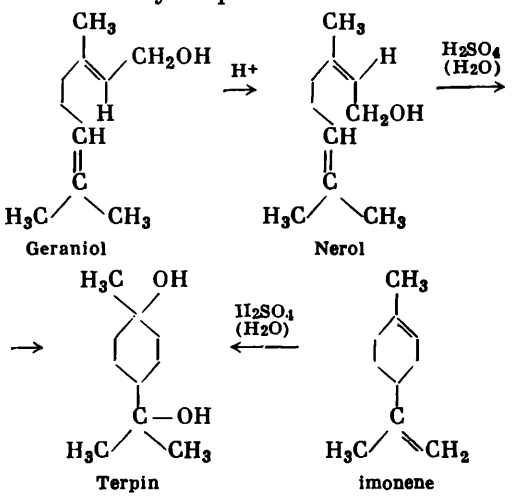


Linalool itself and especially its acetates and hydroxylinalool are widely used in perfumery because they have an odour similar to that of lily of the valley. Citronella oil contains **citronellal**, and rose and geranium oil contain the corresponding alcohol **citronellol**

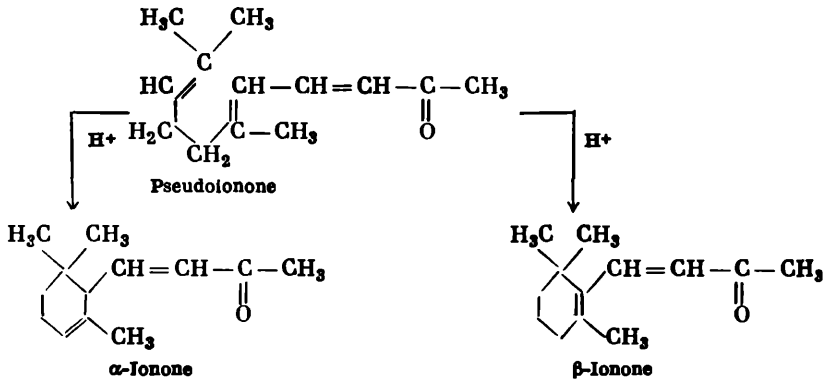


which is also employed in perfumery.

Aliphatic terpenoids readily undergo cyclization. For example, geraniol when reacted with dilute sulphuric acid, being preliminarily transformed into its *cis*-isomer, **nerol**, is hydrated across the double bonds and converted into the monocyclic terpene glycol—**terpin**, which is used in the form of a hydrate as a drug. Terpin is produced industrially by the hydration of the terpene limonene contained in turpentine oil by sulphuric acid:



The croton condensation of citral with acetone gives pseudoionone. This aliphatic ketone when acted on by acid undergoes cyclization and forms the isomeric α- and β-ionones:

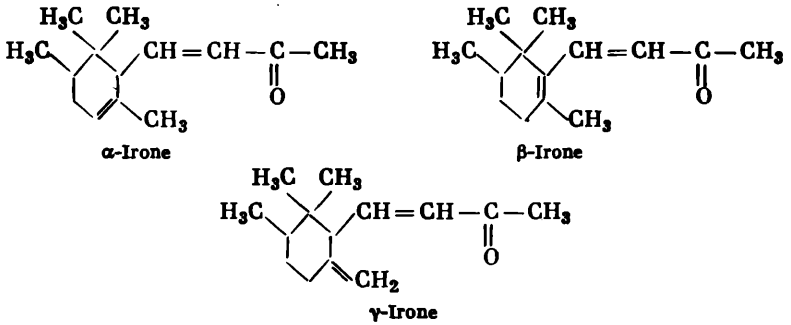


Pseudoionone

α-Ionone

β-Ionone

The ionones smell like cedar wood until they are very much diluted when they exude the pleasant perfume of the violet. They are widely used for the manufacture of scents. The actual odoriferous constituent of violets and also of the irise root consists of the homologues of the ionones, α-, β-, and γ-irones:

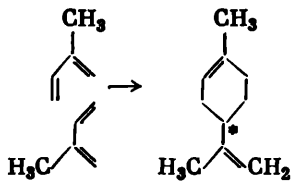


α-Irone

β-Irone

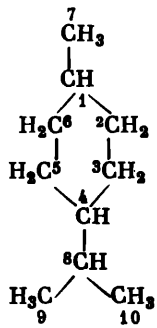
γ-Irone

Monocyclic Terpenes. It has already been mentioned (see Volume I, page 369) that when isoprene is heated in a sealed ampoule, it dimerizes and is converted into **dipentene** (S. V. Lebedev):

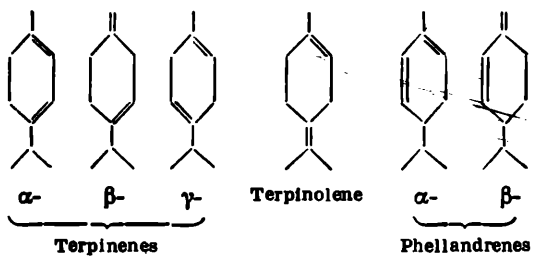


And if dipentene is subjected to cracking, isoprene is formed. Dipentene has one asymmetric carbon atom and racemic dipentene is

obtained synthetically according to the general law. The basic turpentines and the essential oils contain optically active (+)- and (—)-dipentenes, which are known as **limonenes** (they have an odour similar to that of the dried peel of lemon). The catalytic hydrogenation of dipentene leads to a hydrocarbon which is the parent compound for a group of monocyclic terpenes. This hydrocarbon is 4-isopropyl-1-methylcyclohexane or hexahydrocymene commonly known as **menthane**:



The terpenes of the menthane series must evidently have two double bonds, be isomeric to dipentene and be called, like the latter, the **menthadienes.** The following menthadienes are contained in various essential oils:

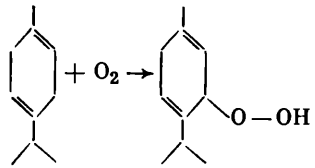


Terpinenes and terpinolene have no asymmetric carbon atom. Naturally occurring phellandrenes are optically active. Their skeleton has been established by catalytic hydrogenation; like their isomer, limonene, they form menthane in this process. Both phellandrenes and α-terpinene can be distinguished from the other isomers by typical reactions of their conjugated π-bonds. Apart from ozonization and oxidation, molecular refraction studies have provided much information concerning the disposition of the double bonds: the presence of a semicyclic double bond, just as in β-terpinene or terpinolene, affects the molecular refraction exaltation by a factor of about 0.5; the presence of conjugated π-bonds, just as in β-phellandrene, gives an even higher exaltation, up to unity; the

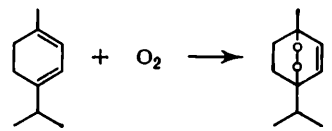
conjugation within the ring, just as in α-terpinene, gives no exaltation. Terpinenes are produced by the isomerization of limonene in the presence of acids.

The terpenes are rather readily oxidized by atmospheric oxygen by two mechanisms, forming peroxides or hydroperoxides.

First, the oxidation may occur at the allylic position:



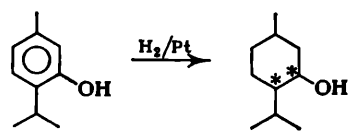
and, second, it may take place across the conjugated double bonds. For example, α-terpinene gives the peroxide **ascaridole**, $C_{10}H_{16}O_2$. The oxidation proceeds as 1,4-addition of molecular oxygen across the conjugated system of π-bonds:



Ascaridole is almost the only peroxide to occur in nature (a constituent of chenopodium oil). It is used as an anthelmintic and as a chain-reaction initiator.

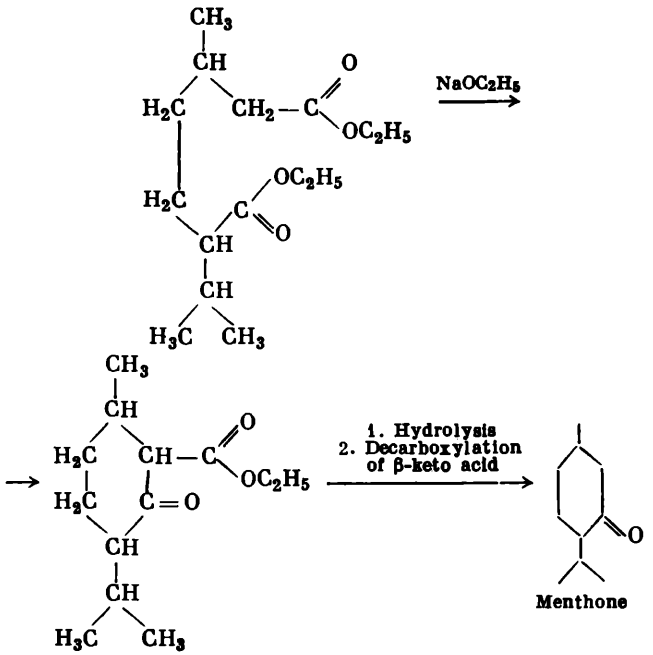
It is precisely because of the formation of peroxides that oils of turpentine speed up the drying-out of oil paints.

Of importance among the oxygen derivatives of menthane is **menthol**—the odorous, chief constituent of oil of peppermint. It forms crystals melting at 43°C and having the odour of mint and is used in the production of tooth powder, pastes, and also in cookery and medicine. The structure of menthol is established by its preparation from 3-methyl-6-isopropylphenol through hydrogenation:

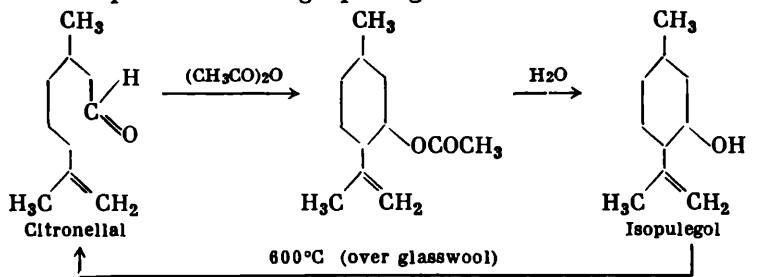


Menthol has two asymmetric carbon atoms. Naturally occurring menthol is levorotatory. The configuration of the natural compound is such that methyl is in the *cis*-, and isopropyl in the *trans*-position to the hydroxyl. The oxidation of menthol gives the ketone **menthone.** It can be synthesized by the internal ester condensation of

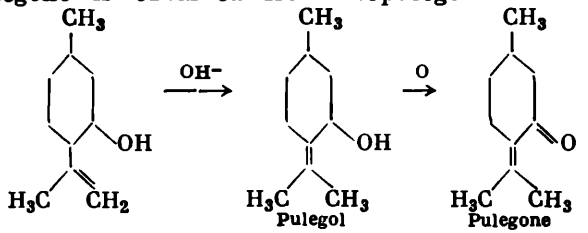
the ester of 1-isopropyl-4-methylpimelic acid:



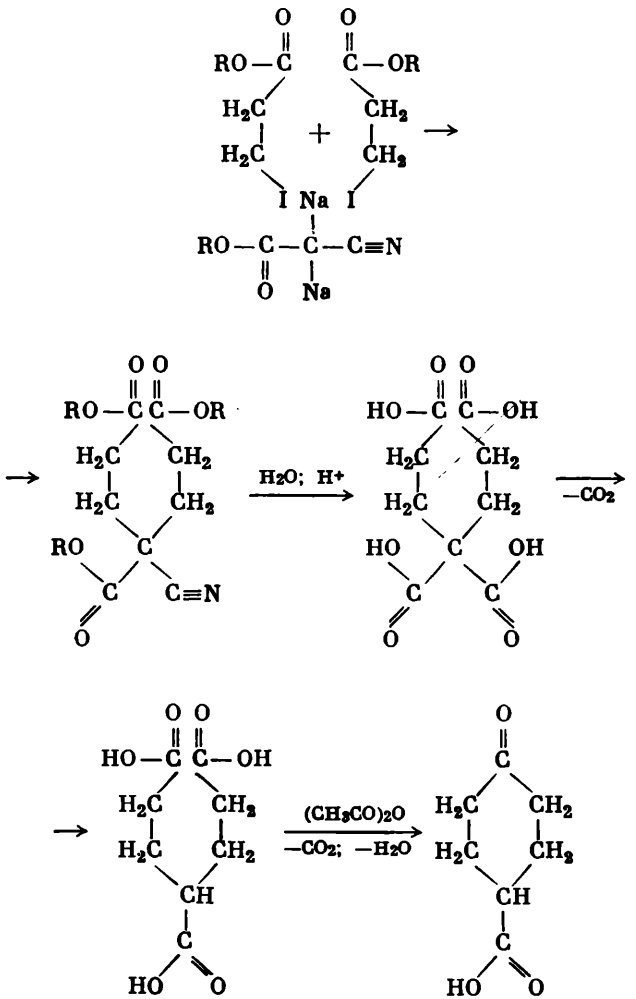
The following scheme of synthesis of an unsaturated isologue of menthone, **pulegone**, affords a new example of the ring closure of an aliphatic terpenoid and ring opening:



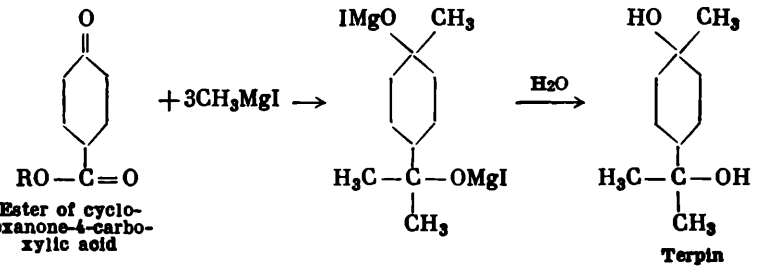
Then, pulegone is obtained from isopulegol:



The above-mentioned glycol **terpin**, $C_{10}H_{20}O_2$, is produced by the hydration of geraniol or limonene in acid medium. We shall cite the Perkin synthesis of terpin: disodiumcyanoacetic ester which will be written in a simplified form (it is evidently an ionic compound with the anionic charge being distributed largely between oxygen and nitrogen) is reacted with the ester of β-iodopropionic acid, the nitriloester formed is hydrolysed and decarboxylated and the two carboxyls of the resulting pentanetricarboxylic acid are subjected to ring closure (acetic anhydride) into cyclohexanone-4-carboxylic acid:



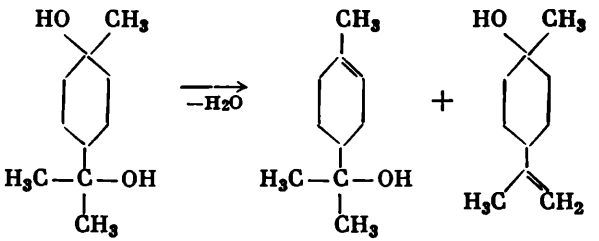
The ester of the resulting cyclohexanonecarboxylic acid is treated with excess methylmagnesium iodide for preparation of terpin:



Ester of cyclohexanone-4-carboxylic acid

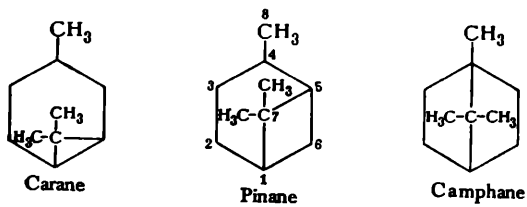
Terpin

When terpin is dehydrated, two isomeric alcohols are formed: α- and β-terpineol which is used in the manufacture of perfumes (it has an odour of lilac):



Terpin α-Terpineol β-Terpineol

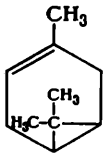
Bicyclic Terpenes and Terpenoids. As pointed out above, bicyclic compounds with the molecular formula $C_{10}H_{16}$ must contain one double bond. On hydrogenation such naturally occurring bicyclic terpenes form the parent, isomeric bicyclic hydrocarbons $C_{10}H_{18}$. There are three such compounds:



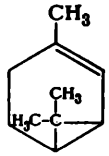
Carane Pinane Camphane

These compounds may be regarded as menthane that has closed the isopropyl group into the bicyclic bridge in the *ortho*-, *meta*-, or *para*-position.

The Carane Group. Two isomeric carenes were found in the Swedish, German (Simonsen) and Russian (B. A. Arbuzov) oils of turpentine:

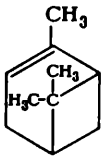


Δ^3-Carene

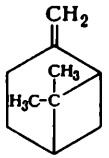


Δ^4-Carene

The Pinane Group. The principal constituent of the turpentine of the pine tree is **α-pinene**. A small quantity of an isomer, **β-pinene** or **nopinene**, is also found in the pine turpentine. It is produced from the fir turpentine.

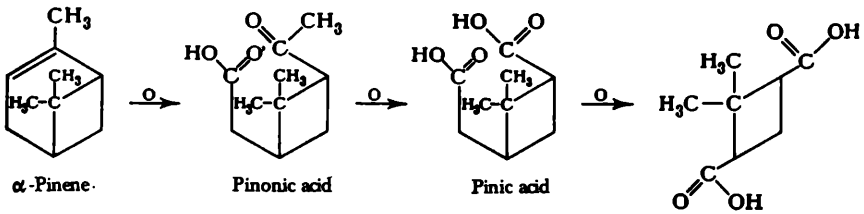


α-Pinene



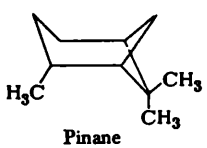
β-Pinene

The structure of α-pinene was determined by Wagner on the basis of degradation through oxidation, the successive stages of which may be briefly represented as follows:

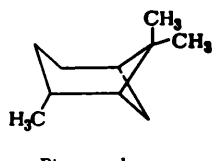


α-Pinene · Pinonic acid Pinic acid

The hydrogenation of α-pinene affords both pinane and its stereoisomer, pinocamphane, discovered by Nametkin:

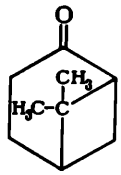


Pinane

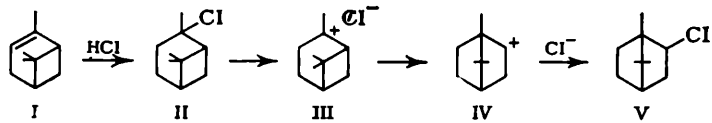


Pinocamphane

β-Pinene when oxidized first gives the ketone



Pinene is capable of many isomerization reactions. For instance: at 350°C it isomerizes, as has already been pointed out, to alloöcimene (see page 306). When pinene is passed at about 300°C over catalysts containing aluminium and titanium oxides, it is transformed into camphene (V. E. Tishchenko, G. A. Rudakov), which is one of the well-known pathways for preparing camphor from oil of turpentine. Finally, a most interesting rearrangement discovered by Wagner occurs when hydrogen chloride is passed into pinene. First, HCl adds on to the double bond in accordance with Markovnikov's rule, following which chlorine is eliminated as the anion. The resulting cation undergoes the retropinacol rearrangement (page 276), in which the pinane skeleton changes to the camphane skeleton and then the chloride ion adds on to the new carbonium ion centre.



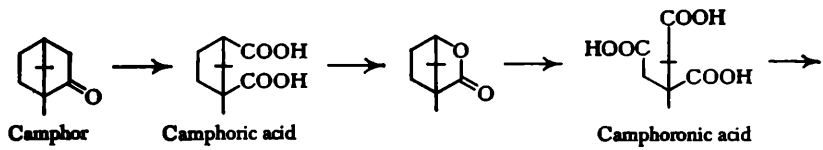
Thus, pinene is converted via the unstable tertiary chloride II into bornyl chloride V, which is a crystalline solid having an odour very similar to that of camphor and which serves as an intermediate product in the synthesis of camphene and camphor by the old method.

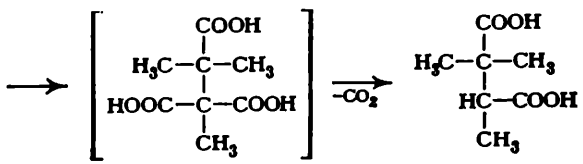
The Camphane Group. Camphane, like its isomers, has not been found in nature. The principal derivative of camphane is **camphor,** an important drug which stimulates the heart activity. Very large quantities of camphor were used for the plasticization of cellulose nitrate and acetate.

Camphor, $C_{10}H_{16}O$, is produced from the leaves of the camphor laurel, *Laurus camphora*, by steam distillation (Japan) and is known as ordinary camphor or "Japan camphor". In this country, camphor is prepared synthetically from pinene by the method developed by V. E. Tishchenko and G. A. Rudakov.

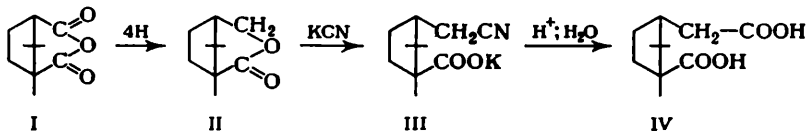
The structure of camphor was established by Bredt. Support for this structure has been obtained by investigations of the products

of its oxidation:

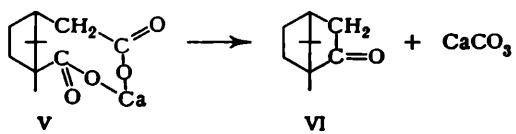




Starting with camphoric acid, Bredt accomplished a partial synthesis of camphor. By reducing camphoric anhydride I, Bredt prepared the lactone, campholide II (the reduction is directed to the carbonyl which is less sterically hindered by the vicinity of the methyl group). With potassium cyanide the lactone underwent ring opening to yield the nitrile III which was then hydrolysed to homocamphoric acid IV. The calcium salt V of this acid, on dry distillation, finally gave camphor VI:

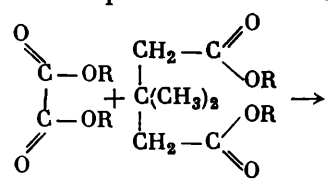


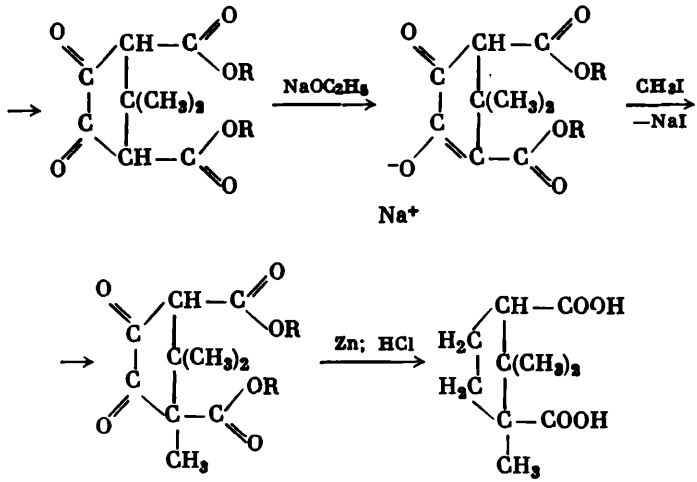
I II III IV



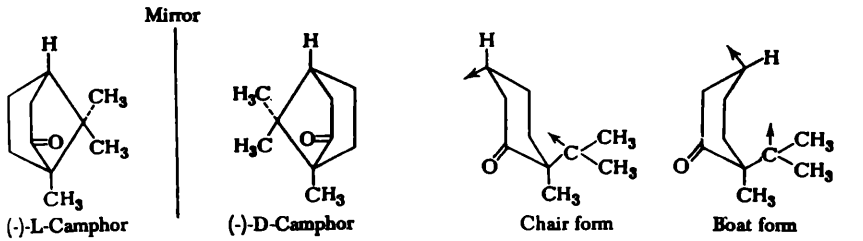
V VI

Later, Komppa synthesized camphoric acid itself ($C_{10}H_{16}O_4$), using the ester condensation of oxalic ester with dimethylglutaric ester. It should be kept in mind that the ester of β-ketonic acid formed by the condensation is capable of exchanging the hydrogen of the group situated between the carbonyl and the carboxyl for sodium. The sodium derivative is methylated to yield diketocamphoric acid, from which camphoric acid is then produced:





Camphor has two asymmetric carbon atoms and, according to the general rule, must have had four stereoisomers, but since two of these must have had a bridge fused at the *trans*-position, which is geometrically impossible, there exist only two stereoisomers, namely, the antipodes D- and L-camphors:

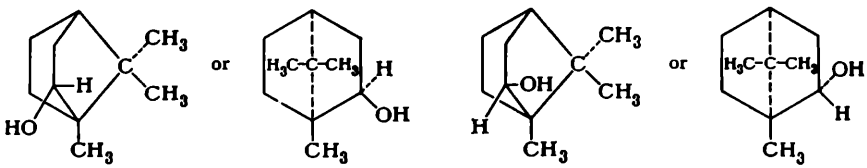


(boat form of cyclohexane ring) (ring closure into the *trans*-position is infeasible)

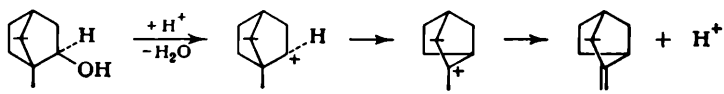
Natural camphor produced from the camphor tree is dextrorotatory; Freudenberg established its intimate stereochemical relationship to D-glucose.

When camphor is reduced to a secondary alcohol, there appears a new asymmetric carbon atom and D- and L-camphor each gives two alcohols: D- and L-**borneols** and D- and L-**isoborneols**. Both antipodes of borneol are found in nature. The isoborneols are considerably more labile than the borneols with respect to the retropinacol rearrangement, which however can be effected on all the four alcohols.

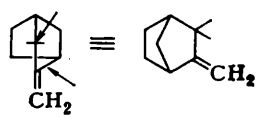
Borneol has the structure with the hydroxyl in the *endo*-position, and isoborneol has its hydroxyl in the *exo*-position:



When these alcohols are reacted with hydroxyl-removing agents, say, with acids (the reaction is especially easily effected with isoborneol), the isobornyl cation left rearranges quantitatively to camphene, ejecting a proton (page 284) and forming a double bond:



The formula of camphene may also be written in a different way:

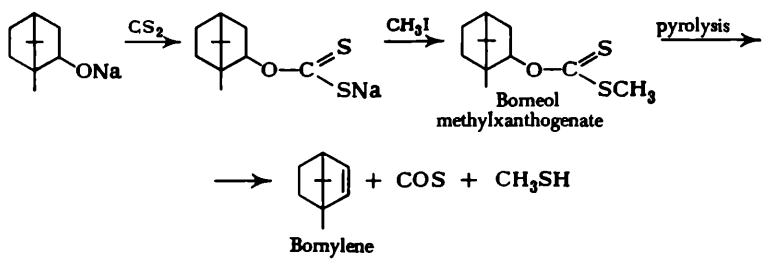


1 2

The members of the camphene ring marked with arrows must be raised above the plane of the paper and bent, as shown in formula 2.

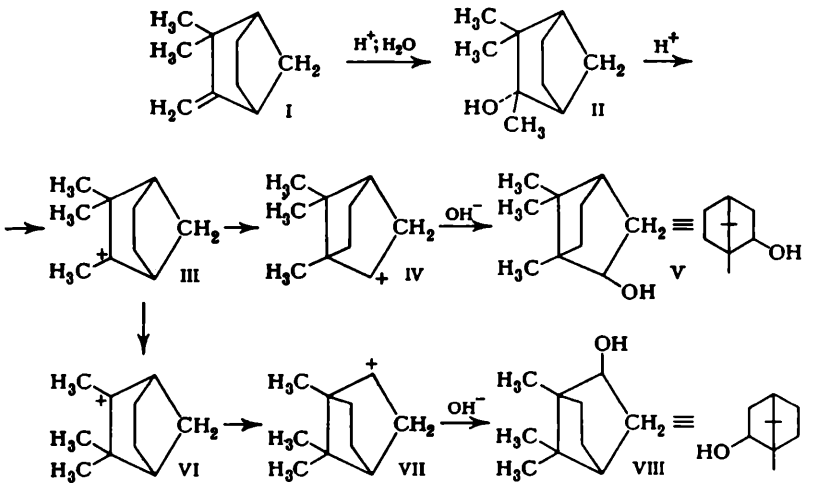
Camphene, $C_{10}H_{16}$, is a terpene with a bicyclic skeleton new to us. The terpene that should have been given the name camphene is called **bornylene**.

Bornylene can be prepared from borneol by the Chugaev method; Chugaev prepared it as follows:



Camphene I, which was prepared by Wagner and later by Meerwein, when reacted with acids (hydration and elimination of OH)

undergoes a retropinacol rearrangement to isoborneol V (the camphene rearrangement of the first kind or the Wagner-Meerwein rearrangement), which has already been dealt with (see page 285). This rearrangement is shown on the first two lines of the scheme. The conversion III → VI starts the Nametkin rearrangement, or the camphene rearrangement of the second kind. The rearrangements lead eventually to two antipodes of isoborneol, V and VIII. The rearrangements proceed via the same carbonium ion III.



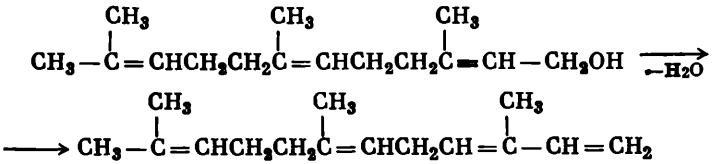
In the Wagner-Meerwein rearrangement, the charge on this carbonium ion is compensated for by the transfer of the bond with rupture of the ring followed by the addition of OH^- to the newly formed carbonium ion centre. In the Nametkin rearrangement, the carbonium ion III compensates the charge by the transfer of the methyl group from the isopropyl bridge, as a result of which on the central carbon atom of this bridge there appears a carbonium ion compensated for by another Wagner-Meerwein transfer of the bond (VI → VII) involving the appearance of a carbonium ion (VII) which then removes OH^- from the medium.

Both rearrangements proceed concurrently but at different velocities, depending on the conditions. Therefore the isoborneol obtained is optically active and partially racemized. That this partial racemization under the conditions of the Wagner-Meerwein rearrangement is accounted for by the rearrangement of the second kind has been proved by Nametkin on 4-methylisoborneol. In the case of this compound, as can easily be seen, the Nametkin and Wagner-Meerwein rearrangements lead to the preparation of structural isomers (cf. page 285).

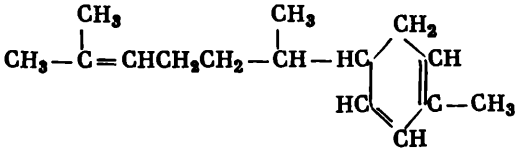
B. Sesquiterpenes and Sesquiterpenoids

The sesquiterpenes include hydrocarbons of the formula $C_{15}H_{24}$, consisting of three isoprene units, and their oxygen derivatives. Like terpenes, these compounds are found widely distributed in essential oils and in plant balsams. Many of them are used in perfumery. We shall confine our attention to a few examples out of the vast number of compounds of this kind that have been studied.

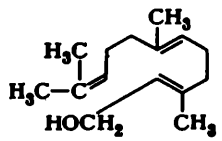
The smell of the blossoming linden tree is due to the sesquiterpenoid **farnesol**. The dehydration of this alcohol gives an aliphatic sesquiterpene, **farnesene**:



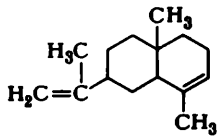
The fragrant matter of ginger oil, **zingiberene**, is a monocyclic sesquiterpene:



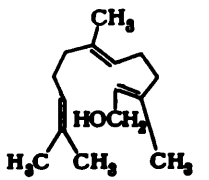
An example of bicyclic sesquiterpenes is **α-selinene**. The scheme given below demonstrates the structural relationship of the aliphatic sesquiterpenoids to bicyclic sesquiterpenoids and azulenes (page 163), which are also found in the essential oils of plants:



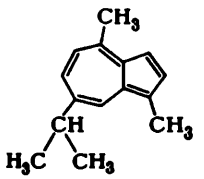
Farnesol



α-Selinene



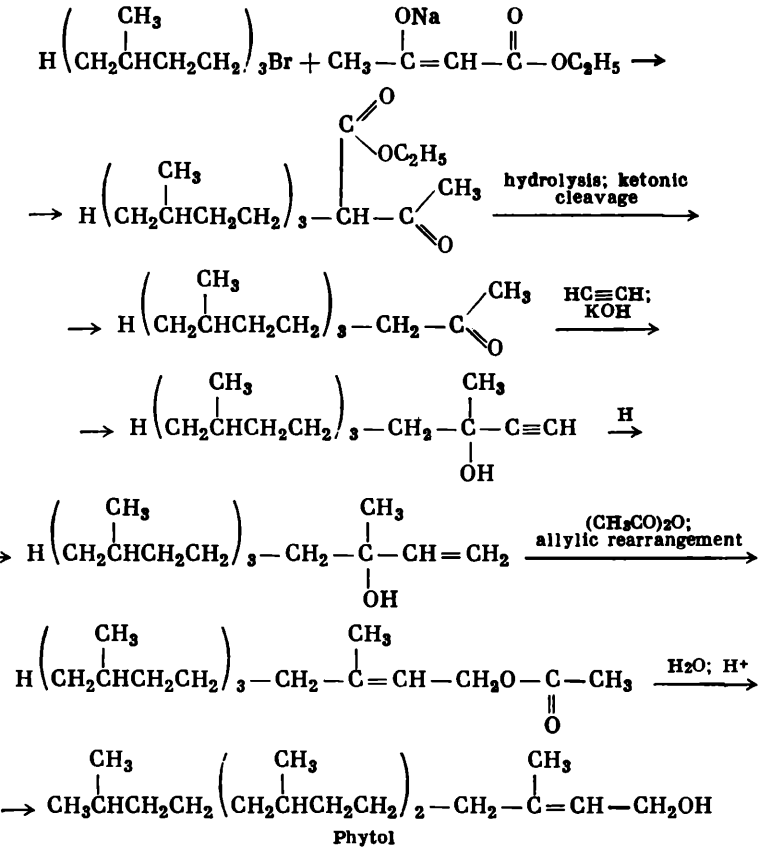
Formula of farnesol written in a different way



Guaiazulene

C. Diterpenes, Tetraisoprenoids, and Carotenoids

Among the tetraisoprenoids with an open chain of atoms mention should be made of **phytol**, an alcohol in the form of an ester, contained in chlorophyls (see Volume I, page 394). The relationship of the phytol skeleton to farnesol is proved by its synthesis from hexahydrofarnesyl bromide (F. G. Fischer):

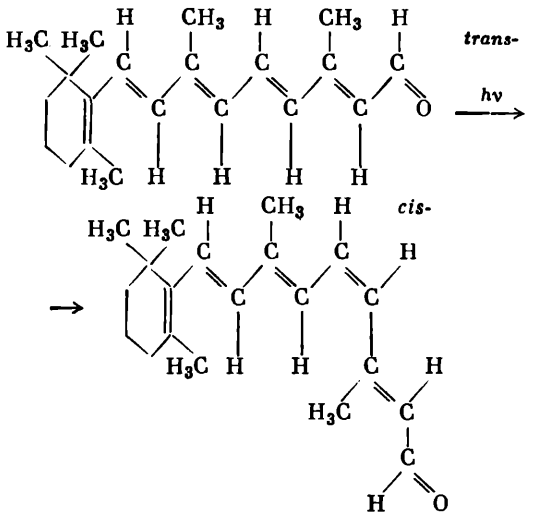


Phytol

Group A vitamins have the tetraisoprenoid skeleton. A continued lack of vitamin A_1 (**axerophthol** or **retinol**) or of the corresponding provitamin, **α-carotene** (see below), in the diet may lead to hardening of the conjunctiva, corneal softening (xerophthalmia) and to complete blindness, weight loss and poor general physical condition, and a deficiency of the vitamin causes night blindness. The latter disease may be accounted for by the fact that vitamin A_1 serves as a source of the photosensitive pigment of the eye, **visual purple** or

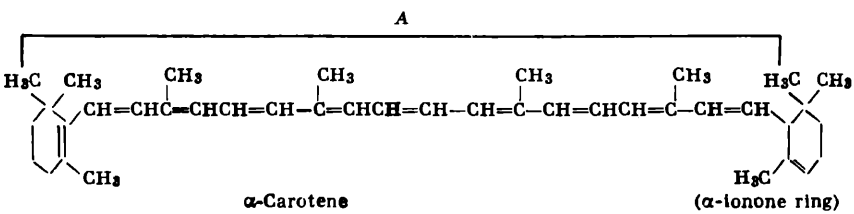
rhodopsin, contained in retinal cones and rods and is responsible for vision, in particular, night vision.

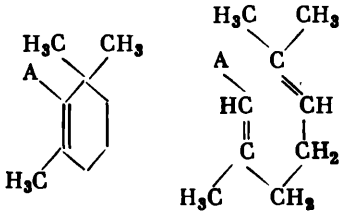
Rhodopsin is the protein opsin linked to retinene (or retinal), which is the vitamin A_1 aldehyde. The chain of retinal has an all-*trans*-configuration. Absorbing a light quantum, retinal bound by rhodopsin isomerizes to 11-*cis*-retinene:

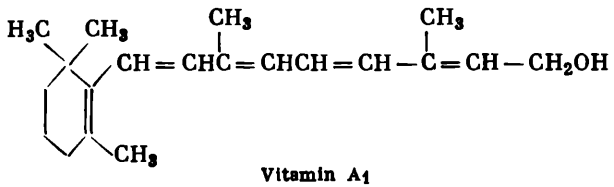


which dissociates from the opsin with liberation of its SH group, which is what triggers the visual process—the conversion of light to nerve impulses. Rhodopsin is a chromoprotein; it is coloured more intensely than retinal. The isomerization of retinal described above takes place only in rhodopsin. The protein here plays the role of a catalyst (enzyme).

Vitamin A_1 is contained in milk and butter, the egg yolk, fish oil; α-carotene (the provitamin of A_1, which is readily converted in the organism into vitamin A_1) occurs in carrots and the green leaves of many plants. Vitamin A_2, which is of less value, contains one double bond more than vitamin A_1. When oxidized in the organism α-, β-, and γ-carotenes form vitamin A_1. The structure of carotenes and their relationship to vitamin A_1 have been largely established by the investigations of R. Willstätter, P. Karrer, and R. Kuhn.



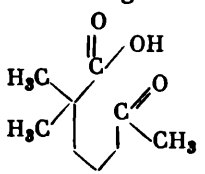




Vitamin A_1

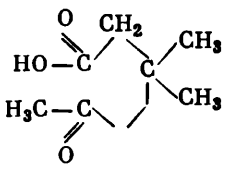
β-Carotene is split in the organism into two molecules of vitamin A_1.

The structure of α-carotene was established by L. Zechmeister, P. Karrer, and R. Kuhn in 1928 on the basis of its oxidation into geronic acid I and isogeronic acid II:



I

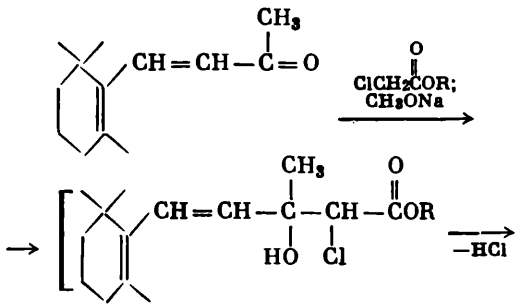
and

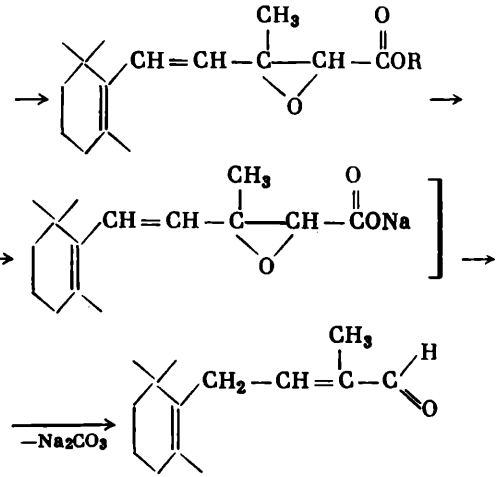


II

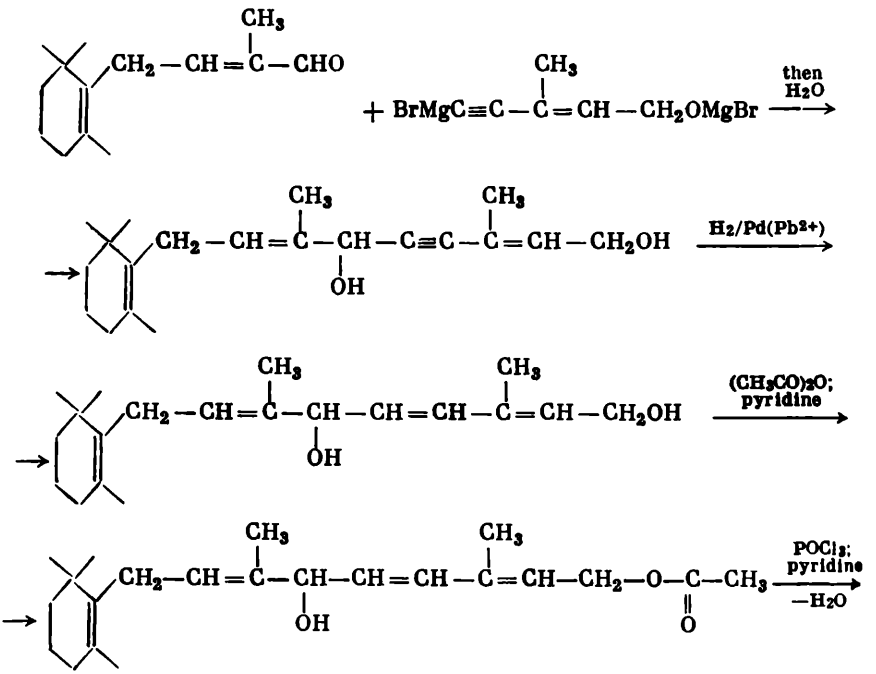
The coloration of α-carotene (dark-red crystals) points to the continuous conjugation chain. The relationships to vitamin A_1 provide much information on the structure of carotenes.

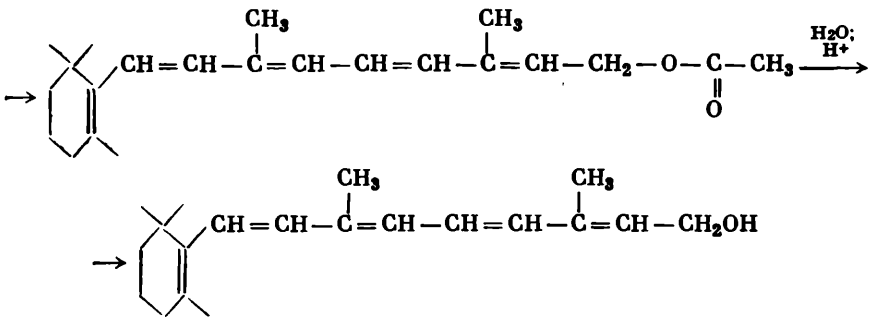
The synthesis of vitamin A_1 which has been carried out in the various ways and which is now effected industrially provides a conclusive proof of the structure adopted. Its synthesis, just as the synthesis of α-carotene, starts from β-ionone. The following is the synthesis of vitamin A_1 accomplished by Isler:





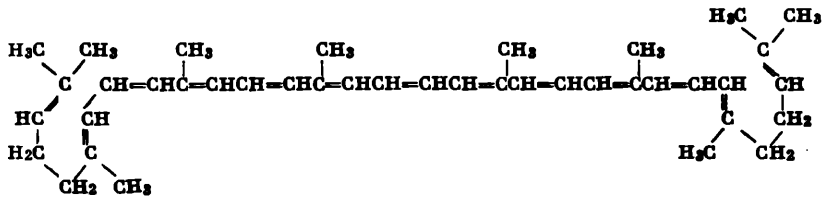
This series of formulas explains the Darzens reaction which proceeds in one step and by means of which β-ionone is built up in this case into the homologous aldehyde. The further synthesis is clear from the following scheme:





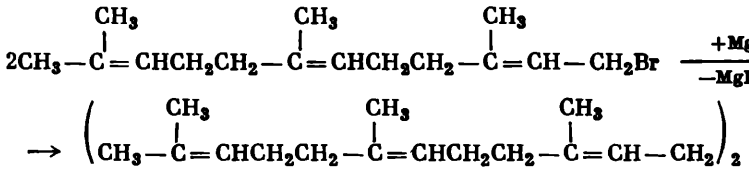
Vitamin A_1

Isomeric with carotenes is the aliphatic hydrocarbon **lycopene**, which is the colouring matter of the ripe tomato and many other plants. The structure of lycopene also includes a long system (namely, 11) of conjugated π-bonds. The following structure of lycopene stresses its relationship to carotenes:



Lycopene

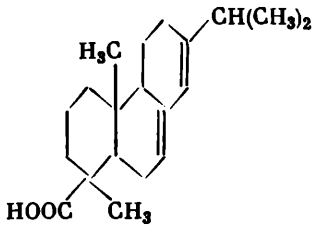
An interesting aliphatic triterpene is **squalene**, which has a close relationship to tetracyclic steroids. This isoprenoid obtained from the shark liver has the structure shown below, which has been elucidated by Karrer through the synthesis from farnesol converted by replacement of OH by Br into farnesyl bromide and doubled by the action of magnesium by means of the Wurtz reaction:



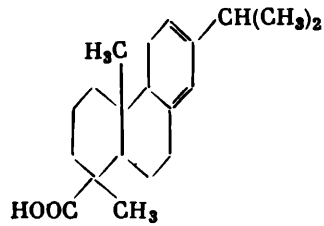
21.2. Resin Acids

It has already been said that the distillation of the resin of conifers yields volatile turpentine oil, leaving the non-volatile residue rosin (*colophonium* or *colophony*), which is a substance having the character of a carboxylic acid and used as an additive to fatty acids

in the manufacture of laundry soap because its sodium salt also has the surface-active properties of soap. Rosin has found other diverse applications. Its salts with manganese and other metals, called **resinates**, are employed as siccatives—additives that initiate oxidation and, hence, also the polymerization of linseed oil in boiling of drying oil (they are soluble in oils). Rosin is used for gluing paper, and forms the component of putties and glues (e.g., Mendeleyev's putty, protective glues from caterpillars). The composition of rosin is $C_{19}H_{29}COOH$; it is a mixture of resin acids—**abietic acid** and **levo-** and **dextropimaric acids.** Below are given the structures of the first two acids, which (especially, abietic) are the chief constituents of rosin:

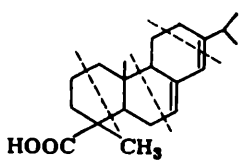


Abietic acid



Levopimaric acid

As can be seen, these acids are derivatives of hydrogenated phenanthrene and in this respect are related to steroids (see below). Indeed, the aromatization of resin acids by the action of sulphur at a high temperature (which involves dehydrogenation into the aromatic system of a substituted phenanthrene, with simultaneous decarboxylation and loss of the angular methyl group in the form of methylmercaptan) yields the so-called **retene** (2-isopropyl-8-methylphenanthrene). This hydrocarbon is formed from resins during the geologic periods and has been found as a fossil. At the same time, abietic acid, like other resin acids (and steroids), is an isoprenoid. This follows from the splitting of its formula:

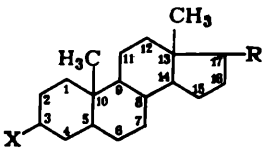


21.3. Steroids

Directly related to isoprenoids are steroids. All steroids have structurally the same cyclic skeleton. They are divided into the following large groups: sterols, bile acids, steroidal hormones, genins (in the form of glycosides occurring in plants and used as cardiostimulants), toad poisons, sapogenins, and steroid alkaloids, which,

in contrast to the other groups, contain nitrogen. We shall confine our attention to the first three groups of the steroids and give only the barest general outline of steroids of the fourth group.

Common to all steroids is the tetracyclic cyclopentanophenanthrene (or cyclopentenophenanthrene) skeleton, the carbon atoms of which are numbered in the manner indicated below: and which in

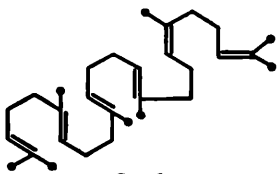


most cases has angular methyl groups at carbons 10 and 13 and a chain of several carbon atoms at carbon 17. In the bile acids, this chain of carbon atoms ends with a carboxyl group, and in genins it assumes the form of an oxygen heterocycle; in hormones there is no such a chain—instead they have a hydroxyl group or a carbonyl oxygen. Besides, there is a hydroxyl group (or a carbonyl oxygen) in position 3.

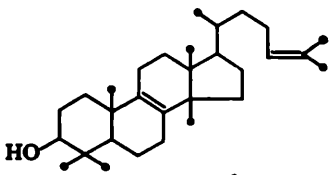
Steroids are extensively distributed in living nature. The alcohols, called **sterols** (from which the name steroid is derived), in which X=OH and R=hydrocarbon residue, are found in animal and plant tissues and play an important, though not yet completely clarified, role. The brain tissue contains up to 7 per cent (on the dry basis) of **cholesterol.** It enters into the composition of animal oils and fats. The deposition of cholesterol in the blood vessels is considered to be responsible for atherosclerosis. The **ergosterol** produced by yeasts is the provitamin of D_2 and is converted into the latter upon irradiation by sunlight, and 7-**dehydrocholesterol** found in the animal organism is the immediate precursor of vitamin D_3. The **bile acids** generated by the liver are necessary for the assimilation of fats. The **sex hormones** secreted by the sexual glands of higher animals (androgenic hormones in the male organism, and estrogenic and gestogenic hormones in the female organism) are responsible for the development of the male and female sexual characteristics and for normal responses peculiar to each sex.

The longest-known steroids are cholesterol, which was first isolated from human gallstones, and the bile acids. Their structure, however, was conclusively elucidated in the thirties of this century only after a tremendous amount of work was done, particularly by Wieland, Windaus and their coworkers. The first female hormone was first isolated in 1929 and the male hormone in 1933 by Butenandt *et al.* This was followed by the rapid and extensive development of the entire field of steroid chemistry, the steroids now constituting a large and specific chapter of organic chemistry.

The intimate relationship between steroids and isoprenoids is established by the proved possibility of biosynthesis of steroids from a typical isoprenoid, squalene (page 325). A comparison of the structure of squalene with that of one of the sterols, lanosterol, spectacularly reveals their close relationship (the dots signify methyl groups):



Squalene

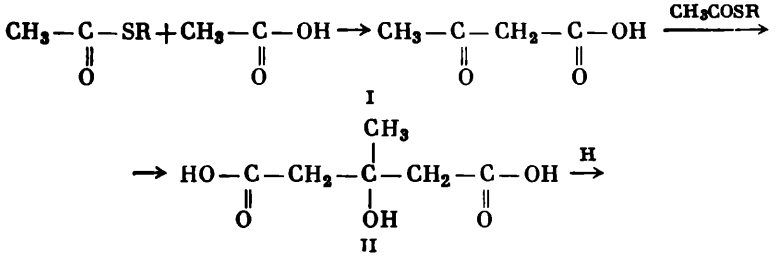


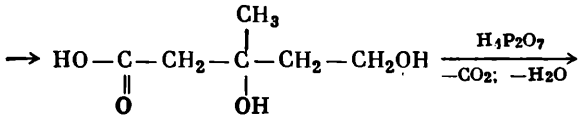
Lanosterol

Apart from the closure of four rings due to the disappearance of four double bonds, the transformation of the squalene skeleton into the skeletal structure of the lanosterol system requires the migration of a methyl group, which is often observed as we know from the chemistry of terpenes.

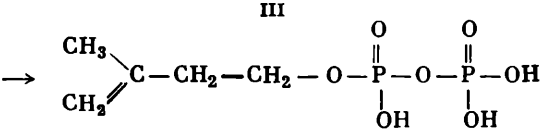
In fact, these complex isoprenoids, like all the isoprenoids, are formed in plants and animals not from isoprene, which has not been found in living organisms, but from acetic acid, which has been reliably established by introducing acetic acid labelled at the methyl group by the radioactive isotope ^{14}C into the plant and animal organisms. This isotope has found to be incorporated into the isoprenoid skeleton. The synthesis of an isoprenoid (e.g., squalene) from acetic acid proceeds according to the scheme, which is reminiscent of the ester condensation, under the influence of a catalyst—the coenzyme A (page 476) designated here as RSH. With acetic acid it is converted into RS—CO—CH_3, which functions as an acetylating agent in biochemical processes.

In this process, the stage at which acetoacetic acid I is condensed as a ketone with a new molecule of acetic acid gives acid II, which is reduced enzymatically to mevalonic acid III. The acid formed loses CO_2 and H_2O and is phosphorylated to isopentenyl pyrophosphate IV, which serves as a building block in the synthesis of isoprenoids.



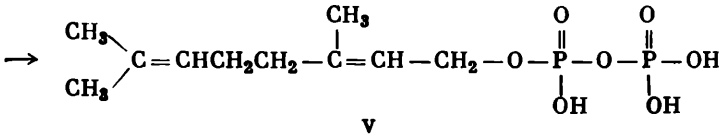


III

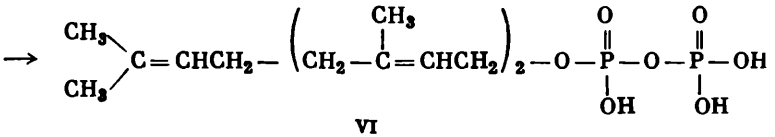


IV

Isopentenyl pyrophosphate IV in the presence of Mg^{2+} and enzymes from yeast (yeast juice) is converted into geranyl pyrophosphate V and farnesyl pyrophosphate VI:

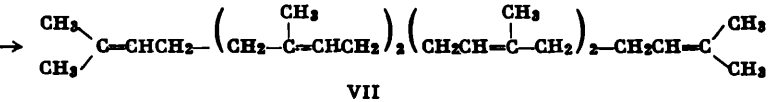


V



VI

Compounds V and VI are converted in the presence of enzymes into squalene VII:

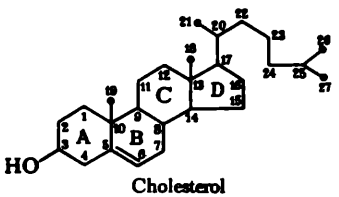


VII

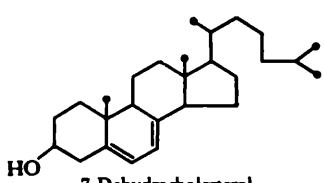
The participation of mevalonic acid has been confirmed by introducing into the organism of labelled mevalonic acid and preparing, as a result, labelled isoprenoids.

A. Sterols (Steroid Alcohols)

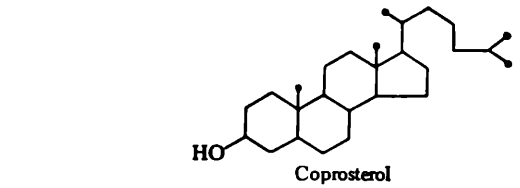
The following are the structures and configurations of certain of the most important sterols of animal (cholesterol, coprosterol) and plant (ergosterol, stigmasterol) origin:



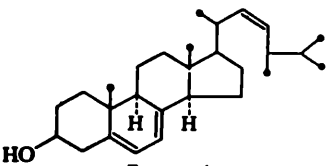
Cholesterol



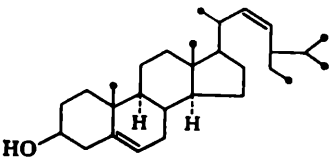
7-Dehydrocholesterol



Coprosterol



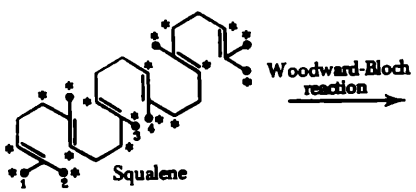
Ergosterol

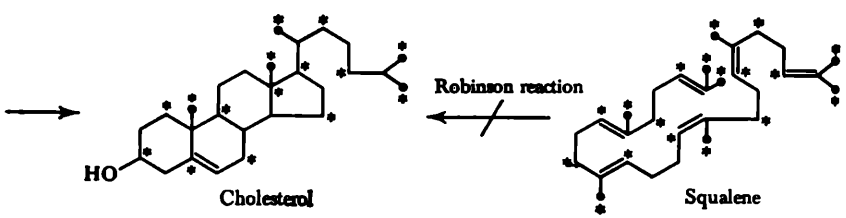


Stigmasterol

The broken lines denote that the substituent or H is situated below the plane of the drawing, away from the viewer (such substituents are designated as α) provided that the methyl group at carbon 10 is above the plane of the drawing. The solid valency lines signify that the substituent or H is situated in the same way as CH_3 at carbon 10—above the plane of the paper, toward the viewer (and is denoted as β). Hence, it is clear that the rings A and B in coprosterol are joined together by *cis*-linkages, and the rings B/C and C/D in all the other four sterols are *trans*-fused (just as in *trans*-decalin, see Volume II, page 257). The question as to the *cis*- or *trans*-linkage, between the rings A and B in the other four sterols is omitted on account of the presence of a double bond between carbon atoms 5 and 6.

Cholesterol is synthesized in the body, like other isoprenoids, from acetic acid, which has been proved by introducing acetic acid labelled at the methyl group into the organism. This tracer experiment also allows one to make a choice between the Robinson and Woodward-Bloch schemes of formation of the cholesterol skeleton by way of squalene; preference is given to the Woodward-Bloch reaction.



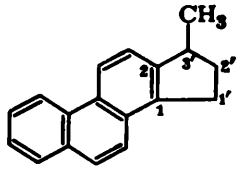


After the cholesterol formed in the body from labelled acetic acid, $*CH_3COOH$, is oxidized under vigorous conditions (according to Kuhn and Roth), there are left only fragments consisting of two carbon atoms (one of them is a methyl group) in the form of acetic acid molecules. According to Robinson, when squalene is converted into cholesterol, the new bonds are formed so that no bond is retained, upon oxidation, between the two labelled carbons and only $*CH_3$—COOH must be formed. According to Woodward and Bloch, there is a possibility of the *C—*C bond being retained (at the angular groups) and, hence, the acid $*CH_3*COOH$ may be formed, which is what actually takes place. As a result of the detailed investigation of the ^{14}C-labelled cholesterol produced in this way the distribution of labelled (originally methyl) carbons shown in the formula has been established. It is evident that the methyl groups of squalene numbered 1, 2, 4 are lost and the group 3 migrates to the second angular position.

Cholesterol has proved to be a key compound in the investigation of many steroids, whose structures have been established from the knowledge of their relationship to cholesterol. We shall therefore confine ourselves to a more detailed interpretation of the structure of cholesterol.

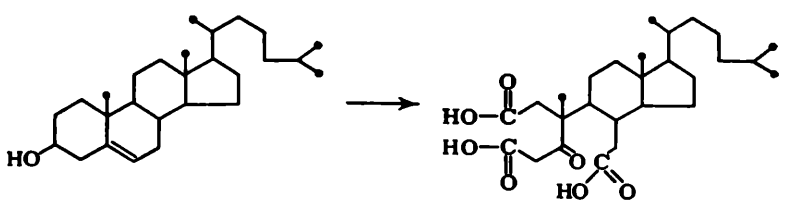
Cholesterol is an unsaturated alcohol and contains one hydroxyl group and one double bond, which is easily established by conventional methods. When subjected to hydrogenation over platinum, cholesterol absorbs 1 mole of hydrogen and forms **dihydrocholesterol** (or **cholestanol**, $C_{27}H_{48}O$), which is stereoisomeric with **coprosterol** (or **coprostanol**). Coprosterol is produced by the hydrogenation of cholesterol in the intestines of animals and is contained in feces. By the replacement of the hydroxyl group by chlorine (PCl_5) in dihydrocholesterol and the elimination of the chlorine ($Na + + C_5H_{11}OH$; first the elimination of HCl and formation of unsaturated cholestene, and then the hydrogenation of the latter) it is possible to convert it into the corresponding hydrocarbon—**cholestane**, $C_{27}H_{48}$, which is stereoisomeric with coprostane formed in this process along with cholestane. It can be prepared in a similar way from coprosterol. Since both cholestane and coprostane have no unsaturated bonds and their molecular formula $C_{27}H_{56}$ differs from the molecular formulas of the isologous paraffins by eight hydrogen atoms, it is clear that cholestane and coprostane are alicyclic compounds consisting each of four rings.

An indication as to the nature of these rings is provided by the dehydrogenation (aromatization) of cholesterol over selenium at 360°C. In this process, the side chain in cholesterol undergoes cracking and the angular methyl groups are removed in the form of methane. This results in the formation of **Diels' hydrocarbon**, $C_{18}H_{16}$ (3′-methyl-1,2-cyclopentenophenanthrene):



Information on the nature of the side chain is provided by the oxidation of cholesterol acetate. Only 2-methyl-6-heptanone, $CH_3CCH_2CH_2CH_2CH(CH_3)_2$ was isolated from the oxidation pro-
‖
O
ducts. The location of the carbonyl group indicates the carbon atom to which the side chain was attached. Had cholesterol, being a tetracyclic monounsaturated alcohol, only an octane side chain, its molecular formula would be $C_{25}H_{42}O$, but in fact its formula is $C_{27}H_{46}O$, i.e., it contains two more CH_2 units. Thus, apart from the side chain (2-methyl-6-heptanone), cholesterol contains two side methyl groups (or one ethyl group). The position of the long side chain at carbon 17 in cholesterol and other sterols follows from the oxidative degradation of some of these compounds to sex hormones (the reaction is described below). In this process, the long side chain undergoes degradation and the result is the formation of a carbonyl oxygen at the point of attachment of the chain. This is exactly position 17. As regards the two CH_3 groups, it follows that, since they do not remain attached to the aromatic nuclei and are eliminated as methane, they must be quaternary (angular) methyl groups. It is only in this case that aromatization cannot be accomplished by dehydrogenation alone; the elimination of the side chains is required too. The exact position of the side chains is established only by the oxidative degradation. The degradation also provides information on the positions of the hydroxyl group and double bond in cholesterol. A new, stricter evidence is obtained, confirming the size of all the four component rings of cholesterol and their stereochemical *cis*- or *trans*-fusion.

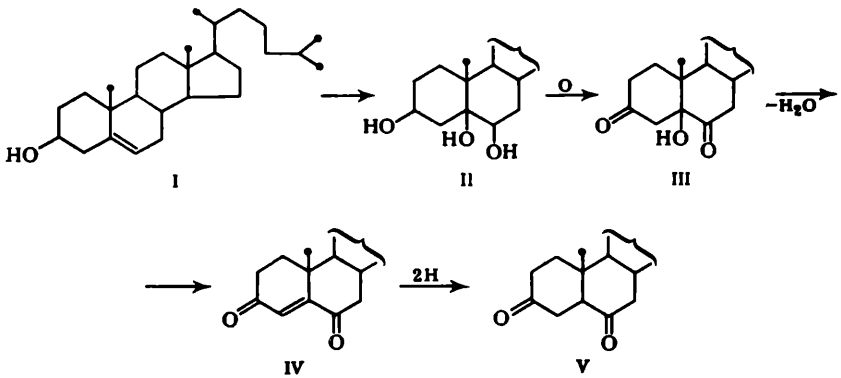
The oxidation of cholesterol leads, in particular, to a bicyclic tricarboxylic keto acid:



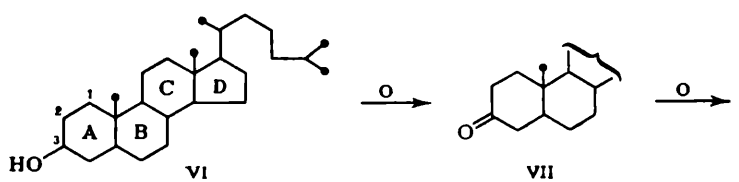
Since the oxidation is directed, in the first place, to the double bond and the secondary alcoholic group (a ketone is formed, which

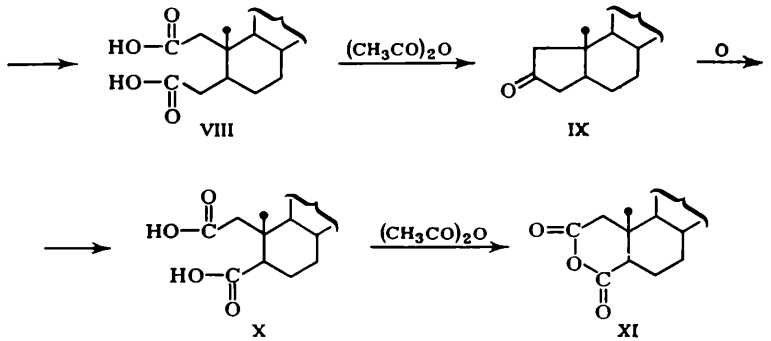
gives a dicarboxylic acid), it becomes clear that the formation of the tricarboxylic acid indicates that the hydroxyl group and the double bond in cholesterol are in different rings.

The fact that the double bond is situated in the β-γ position with respect to the hydroxyl group is proved as follows. When the double bond is cautiously oxidized with permanganate by the Wagner method, cholesterol is converted into triol II, which is further oxidized into dione-ol III, one of the alcoholic groups of the starting triol (probably, tertiary) not being oxidized. When this group is dehydrated and the resulting unsaturated diketone IV is hydrogenated to a saturated diketone V, supporting evidence is obtained, based on the typical reactions, indicating that this is a 1,4-diketone. Since the hydroxyl group eliminated by dehydration was tertiary and, hence, occupied an angular position, the relative disposition of the hydroxyl group and double bond in cholesterol is thus determined.



But it is necessary not only to determine the relative position of the hydroxyl group and double bond (the distance along the chain of carbon atoms) but also to find out at which carbon atom the hydroxyl group is situated and thus to determine the position of the double bond. This problem may be solved on the basis of the oxidative degradation of dihydrocholesterol VI (cholestanol) and cholesterol, which provides an additional evidence that ring A is the cyclohexane ring.

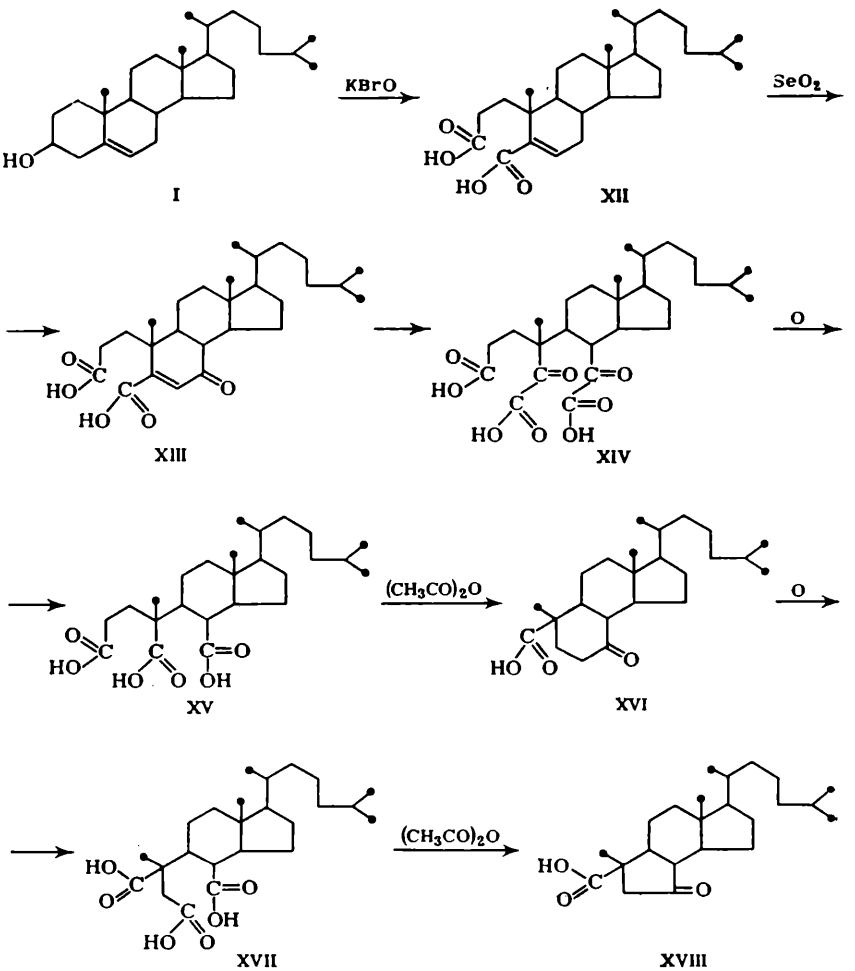




The ketone VII produced by the oxidation of dihydrocholesterol VI is further oxidized to dicarboxylic acid VIII. The presence in this acid of four α-hydrogen atoms, i.e., of two methylene groups to which the carboxyls are attached, can be proved in various ways. Hence, the hydroxyl group in cholesterol may be at position 2 or 3. The fact that under the influence of acetic anhydride the acid VIII forms a ketone (with the loss of CO_2 and H_2O) and not the anhydride of a dibasic acid proves that the hydroxyl-bearing ring A is six-membered; otherwise, had this acid been a derivative of glutaric acid rather than of adipic acid, the given reaction would have led to a derivative of glutaric acid and not to a ketone. This is a general method which enables one to distinguish between six-membered and five-membered (and lower) rings. That the compound IX is a five-membered ketone is proved by its oxidation to a derivative of glutaric acid, which undergoes ring closure not to a ketone but to anhydride XI.

Cholesterol I can be oxidized by means of KBrO with opening of ring A, the double bond being unaffected; this gives a dicarboxylic acid XII which has one mobile methylene unit (α-CH_2). Upon further oxidation with SeO_2 the acid XII is converted into keto acid XIII, which undergoes oxidation with the loss of the double bond (hence, with the opening of ring B) to bis-α-keto acid XIV having three carboxyls. That both keto-acid groupings are α- rather than β-keto-acid groupings is easily determined by means of characteristic reactions and indicates that the hydroxyl group is situated at carbon 3 in ring A. It can easily be proved that if the hydroxyl group were at carbon 2, one of the keto-acid groups would possess α- and the other β-keto-acid character. Upon further oxidation of compound XIV two carboxyls are burned away (to give CO_2) and a tricarboxylic acid XV is formed, which undergoes cyclization with simultaneous decarboxylation to give the keto acid XVI.

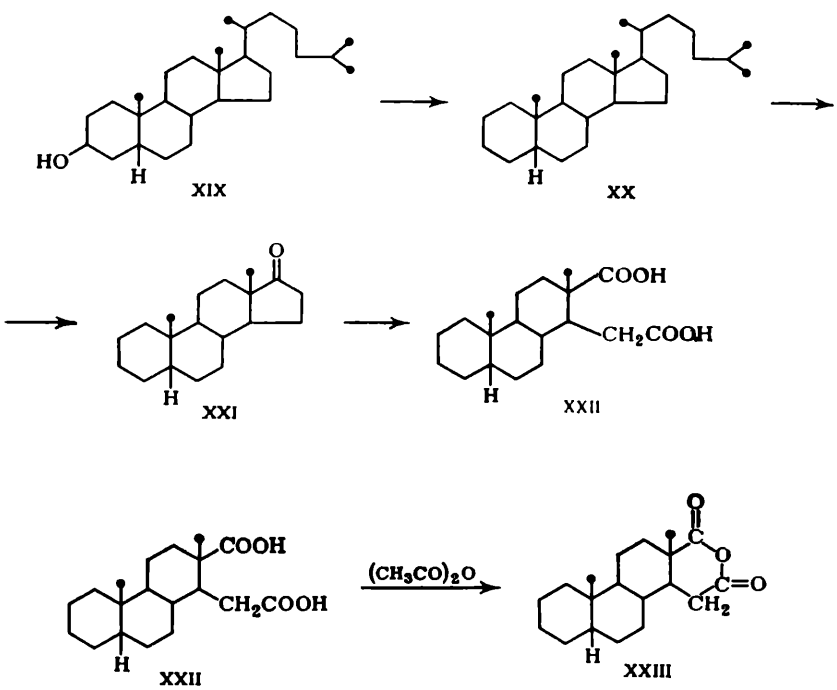
The oxidation of keto acid XVI gives a tricarboxylic acid XVII, which also undergoes cyclization under the influence of acetic anhydride to form keto acid XVIII.



The keto acid XVIII contains a carbonyl group in the five-membered ring, which can be established by its oxidation with opening of this ring to give a tricarboxylic acid capable of cyclization to form an anhydride and not a ketone. From this it follows that keto acid XVI contained a carbonyl group in the six-membered ring and, hence, the carboxyl groups in tricarboxylic acid XV that took part in the cyclization were separated by seven carbon atoms (one of these seven carbon atoms is removed upon cyclization in the form of CO_2). Consequently, formula XIV must belong to an α,α-diketonic acid and formula XIII must correspond to the previous stage of oxida-

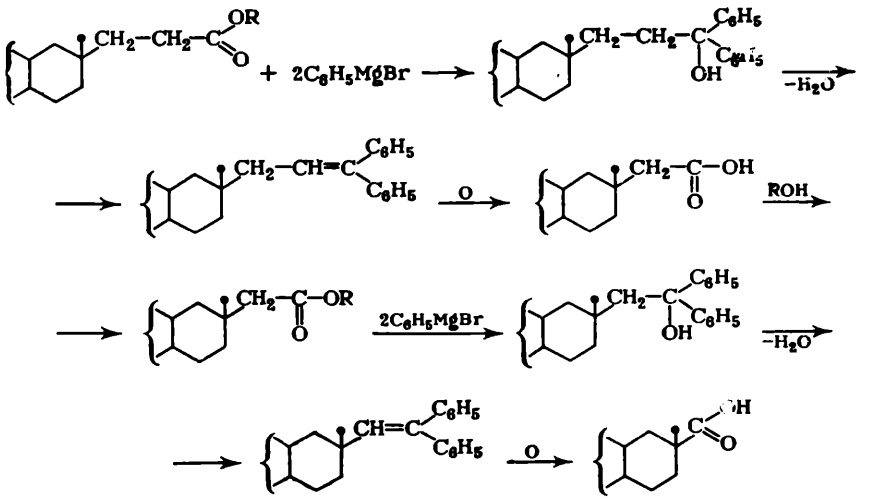
tion, which still retained the double bond of cholesterol. In this way the six-membered structure of ring B in cholesterol is established.

The five-membered structure of ring D is confirmed by the following reactions. The hydrogenation product of cholesterol, coprosterol XIX, is converted into the corresponding hydrocarbon coprostane by the replacement, in coprosterol, of the OH group by Cl (under the action of PCl_5) and of the chlorine by hydrogen (Na in the alcohol). Coprostane XX when oxidized gives 17-testanone XXI which upon further oxidation affords the dicarboxylic aetiobilianic acid XXII. The cyclization of this acid yields anhydride XXIII rather than a ketone. Hence, ring D was five-membered.



What has been said is quite enough for understanding the principles of elucidating the structure of steroids by way of oxidative degradation. The position of the methyl groups is also clarified by this series of reactions. Of much help in this connection is the Barbier-Wieland degradation. This method offers a means of "stepping down" a carboxylic acid by one CH_2 unit.

The Barbier-Wieland method may be illustrated by the following set of reactions:



The resulting acid contains a carboxyl group at a quaternary carbon atom, which follows from the impossibility of further contraction of the number of carbon atoms by the Barbier-Wieland method. In this way the position of the quaternary carbon atom (and, hence, of the angular methyl group) is established.

B. The Configuration of Steroids

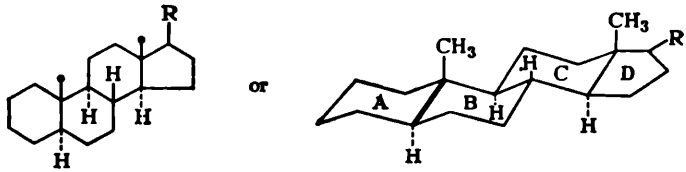
The tetracyclic skeleton of steroids containing no double bonds can be built up on the basis of *cis*- or *trans*-union (just as in the case of *cis*- and *trans*-decalins) of each pair of rings, A and B, B and C, and C and D. As an example, we may cite stereoisomeric hydrocarbons corresponding to cholesterol—cholestane and coprostane (see page 338).

In the formulas of the stereoisomers given below, the hydrogen atoms and methyl groups are shown, relative to which the *cis*- and *trans*-positions are considered.

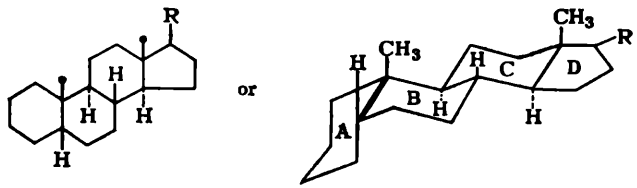
In ring A in cholestane, the heavy line designates the C—C bond relative to which the rings A and B are in the *trans*-position; in coprostane, the heavy line signifies the bond relative to which the rings A and B are in the *cis*-position.

The problem of the *cis*- or *trans*-fusion of rings A, B, C, and D is solved in several ways.

1. By oxidative degradation. The fact that the oxidation of cholestanol VI (page 333) gives acid VIII, in which both HO—CO—CH_2— groups are in the *trans*-position to each other, proves the *trans*-deca-



Cholestane *(trans-, trans-, trans-)*



Coprostane *(cis-, trans-, trans-)*

lin disposition of rings A and B in cholestanol. It is apparent that such a reaction with coprosterol must lead to the *cis*-stereoisomer of acid VIII. The problem is thus reduced to establishing the *cis*- and *trans*-configuration of substituted cyclohexanes.

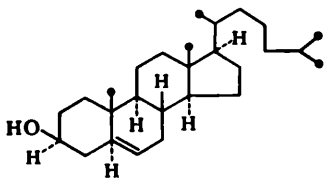
2. By determination of the arrangement of atoms by means of X-ray examination. This painstaking (at that time) method was used in the investigation of cholesterol (D. Crowfoot and C. H. Carlisle, 1945).

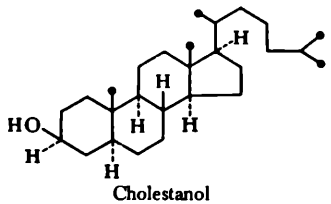
3. By establishment of the stereochemical relationship between the steroid under study and a reference compound of known stereochemistry, say, cholesterol. Such a relationship is deduced from the identity of the degradation products in the corresponding conversions.

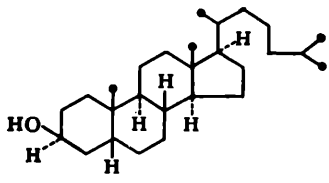
4. Some information can be gained on the basis of the rough additivity of molecular rotation of the polarization plane.

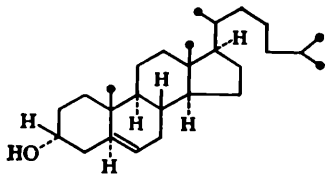
Apart from the stereochemistry of the skeleton, the steroids are also characterized by the stereochemistry of the arrangement of substituents. Thus, the hydroxyl group of cholesterol and coprostanol may be attached either *cis* or *trans* to the nearest angular methyl group (at carbon 10). The substituent which is in the *trans*-position with respect to the nearest angular methyl group is designated by the letter α, and one in the *cis*-position by β. In formulas, the angular methyl group is conventionally assumed to lie above the plane of the ring, i.e., a full line is used to link it to the ring; the same is done for β-substituents (*cis*-), and α-substituents (*trans*-) are connected to the ring by a broken line. Compounds that are stereoisomeric with a given compound are said (according to the position of the substituents) to belong to the *epi* series (epicholesterol, epicholestanol, etc.); the prefix *epi* indicates the epimer due to the inversion of the configuration of C_3.

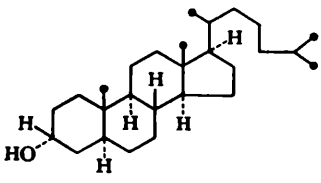
The following are some examples:

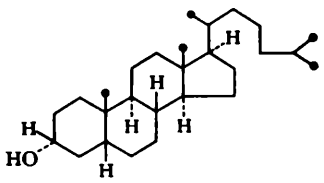

Cholesterol


Cholestanol
(dihydrocholesterol)

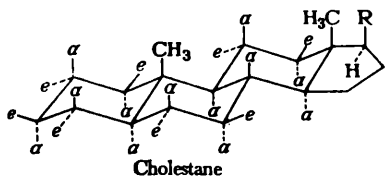

Coprosterol
(coprostanol)

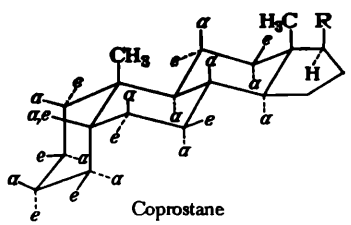

Epicholesterol


Epicholestanol


Epicoprosterol

The simplest route for determination of the stereochemistry of the hydroxyl group (*cis*- or β-, *trans*- or α- with respect to the nearest angular methyl group) is associated with the conformation of the steroid molecule and with the equatorial or axial position of the hydroxyl group. In the formulas given below, the substituent groups in the skeletons of cholestane, a hydrocarbon corresponding to dihydrocholesterol, and coprostane, a hydrocarbon corresponding to coprostanol, are classified into equatorial (*e*) and axial (*a*):


Cholestane

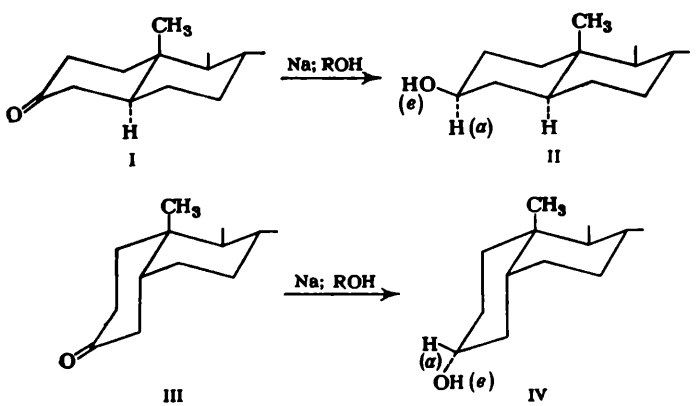

Coprostane

Substituents enter and leave the equatorial and axial positions with different ease. This is accounted for by the fact that the equato-

rial substituents lying close to the (average) plane of the ring are more remote from the neighbouring atoms and the steric hindrances affect little their entry. Incidentally, in contrast to the aliphatic series, the conformation of the tetracyclic skeleton is fixed and the position of the *a*- and *e*-substituents is permanent.

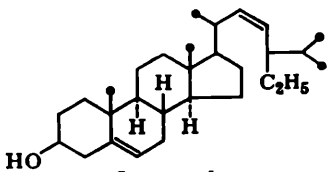
With cyclohexane derivatives there have been found a number of reactions that differentiate the entry of axial and equatorial substituents and their elimination. Thus, the reduction of cyclohexanones with sodium in alcohol leads to the formation of an equatorial group, and the catalytic hydrogenation with hydrogen rather often gives rise to an axial substituent. Dehydration with acids occurs more readily with the hydroxyl group being in the axial position, etc.

Therefore, the ketone resulting from the oxidation of dihydrocholesterol, 3-cholestanone (I), with its carbonyl group being reduced by sodium in alcohol gives dihydrocholesterol II with an equatorial arrangement of the OH group, which, as seen from the scheme, is the *cis*-position with respect to the nearest angular methyl group. In this way it is found that cholesterol has the configuration of 3-β-cholestanol. In a similar way, the oxidation product of coprostanol, 3-coprostanone (III), is reduced to alcohol IV; in this case too the hydroxyl group occupies an equatorial position. As seen from the scheme, this equatorial substituent in this particular case is in the *trans*-position with respect to the nearest angular methyl group, i.e., the configuration of alcohol IV thus obtained is expressed by the term 3-α-coprostanol:

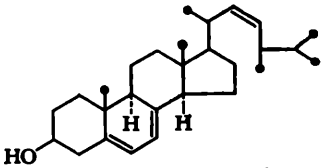


Apart from the sterols described above, mention should also be made of the sterol of soya beans, **stigmasterol** ($C_{29}H_{47}OH$ or $C_{29}H_{48}O$), which has the same configuration as cholesterol but differs from the latter in constitution of the side chain; **ergosterol**, $C_{28}H_{44}O$, which is contained, for example, in yeasts, mushrooms, wheat sprouts and

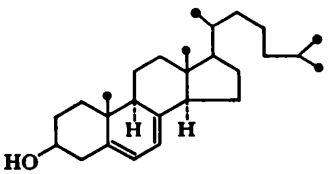
which is especially interesting in that it is the provitamin of D_2; and **7-dehydrocholesterol** (formula as for cholesterol, but with an additional double bond at the 7,8-positions), which is the provitamin of D_3.



Stigmasterol

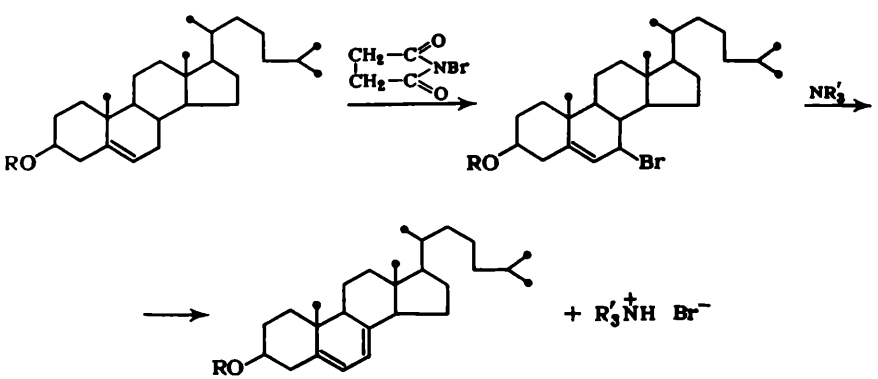


Ergosterol (provitamin D_2)



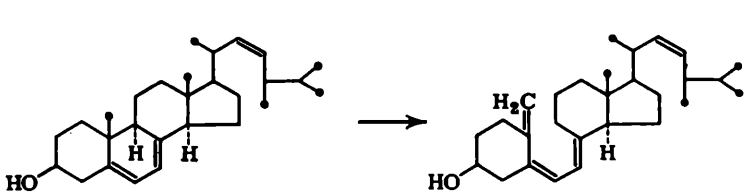
7-Dehydrocholesterol (provitamin D_3)

7-Dehydrocholesterol is an animal sterol (sterols of animal origin are called **zoosterols**) and is contained in the skin and nerve tissues of animals and it is present in high concentrations in mollusc shells. It can be obtained synthetically from the ester of cholesterol by brominating the latter with bromosuccinimide (this is a homolytic bromination—bromine enters the allylic position) and by eliminating HBr with a base:



When irradiated with ultraviolet light ergosterol and 7-dehydrocholesterol (in the free state or in the organism) are transformed into their isomers—ergocalciferol or **calciferol** (vitamin D_2) and **cholecalciferol** (vitamin D_3), both having nearly the same activity. These are the most potent of the vitamins of the D group. Vitamin D is the term applied to a number of fat-soluble substances which are the essential constituents of the human (and animal) diet, their function being the control of the assimilation of calcium and the growth of bones and teeth. A deficiency of vitamins D in the young organism causes the disease known as "rickets" (the *English disease*), a condition characterized by softness and distortion of bones.

The other D vitamins are considerably less active and differ from one another only in the constitution of the side chain, which varies depending on the corresponding sterol. When the provitamins are irradiated, ring B is opened and a third double bond appears, being in the conjugated position with respect to the other two double bonds which are also conjugated. For ergosterol (the provitamin of D_2), the process may be represented in the following way, the intermediate stages being omitted:



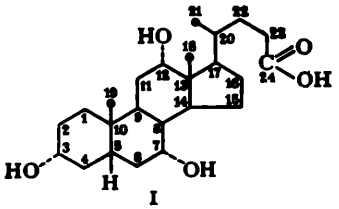
The daily dose of vitamins D (D_2 or D_3) in the North is 7-12 μg for adults and 17-25 μg for children; it is considerably higher for rachitic patients.

High concentrations of vitamins D are present in fish-liver oils, especially in mackerel-liver oil. They are also contained in butter, milk, eggs (yolk), mushrooms. At present vitamins D are isolated from the non-saponifiable portion of the fish or whale oil or is prepared by the irradiation of the provitamins.

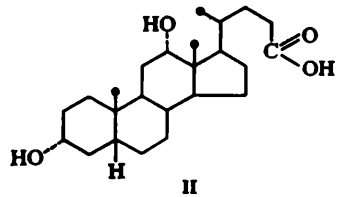
C. The Bile Acids

The bile acids form the main constituents of the bile or secretion of the liver in vertebrate animals. For example, the bile of man contains **cholic acid** I, **desoxycholic acid** II (or deoxycholic acid), **lithocholic acid** III, and other acids. These are monocarboxylic hydroxy acids with the same skeleton but differing in the number of

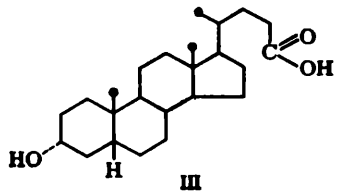
hydroxyl groups:



I

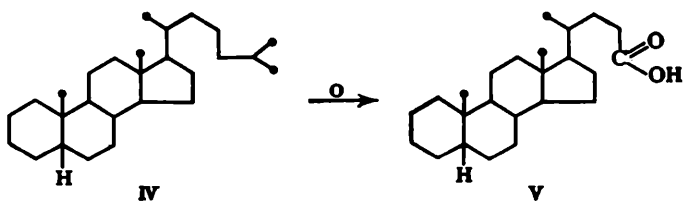


II



III

When the hydroxyl groups in all these acids are replaced by hydrogen (for example, by dehydration followed by the hydrogenation of the double bonds formed), the acids are converted into cholanic acid V, which in its turn was prepared by Wieland by the oxidation of coprostane IV:

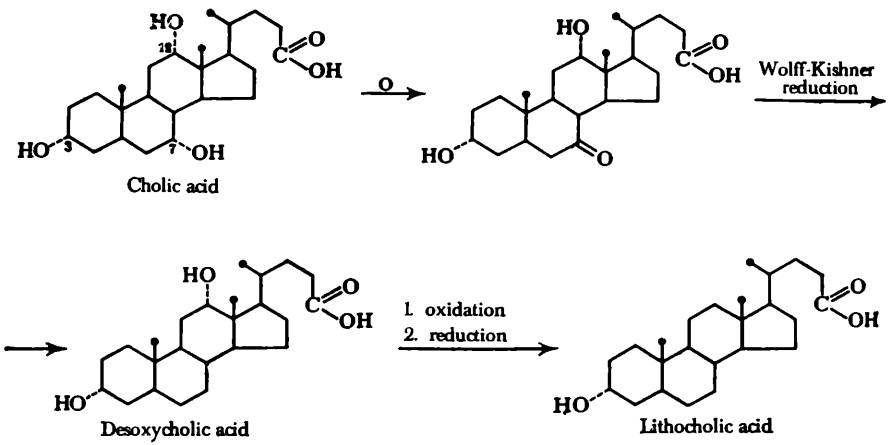


IV V

In this way it has been found that the bile acids have the same cyclic skeleton, which is also identical with the skeleton of coprostane, i.e., have the same *cis*-junction between rings A and B and *trans*-fusion of the rings B/C, and C/D, and also the same position of the side chain at carbon 17 and the same constitution of the chain.

In these acids, only the hydroxyl group at carbon 3 is equatorial, all the other hydroxyl groups being axial. The equatorial hydroxyl group is acylated much more readily than the axial hydroxyls and can therefore be protected by acylation. On the other hand, it is oxidized the most difficultly. The most readily oxidized is the axial hydroxyl group in position 7, and therefore on cautious oxidation it can be oxidized to a carbonyl group and then reduced by the Wolff-Kishner reaction to a CH_2 group. This yields desoxycholic acid.

When this procedure is repeated, the same will happen to the hydroxyl group in position 12, which will lead to lithocholic acid:



The bile acids, the most important of which is cholic acid, are produced in the liver. They are contained in the bile in the form of compounds acylated by cholic acid—glycine, $H_2NCH_2CO_2H$, and taurine, $H_2NCH_2CH_2SO_3H$, e.g., **glycocholic acid** (=glycine + cholic acid) and **taurocholic acid** (= taurine + cholic acid). They play an important role in the digestion and absorption of fats which are emulsified by them. The ability of the bile acids to form molecular compounds with fatty acids is of importance here. Genetically, the bile acids are related to cholesterol. By introducing labelled cholesterol into the organism, it is possible to trace the formation of labelled bile acids.

D. The Steroid Hormones

The Sex Hormones. The concept of the endocrine glands as the organs producing physiologically active substances called hormones, which are secreted into the blood stream and serve to regulate the diverse physiological functions associated with metabolism, was introduced into science in the middle of the last century by Claude Bernard. The long-known undoubted fact that the male and female gonads also play the role of endocrine glands (testes in the male and ovaries in the female) was proved directly only in 1930 by the isolation of the corresponding hormones, elucidation of their specific action and, later, by the determination of their structure.

The sex (male and female) hormones have been found to be alcohols, phenols or ketones (or hydroxy ketones) with the cyclopente-

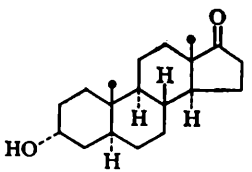
nophenanthrene skeleton. The search for these hormones and their isolation are associated with the elaboration of biological tests and with the quantitative estimation of the content of these compounds by their physiological action. The male sex hormones are extracted from the testes (testicles) or from male urine where they are contained in exceedingly small amounts. They are able to induce the secondary male sexual characteristics in castrated immature males. For example, castrated cocks have an undeveloped comb and the general appearance of the hen. The injection of androgeno-active (i.e., possessing the properties of the male sex hormones) solutions into their blood induces the rapid growth of the comb (wattles, tail, spurs) and the development of the adequate appearance. There have been established the quantitative relationships between the rate of growth of the comb and the content (and activity) of the hormone. By subjecting the hormone extracts to enrichment through the extraction of the hormone source it is possible to trace the increase of the extract concentration by means of biological assays. Using the methods of biological assay, Butenandt et al. in 1931 extracted 15 mg of an individual crystalline substance from 25 tons of male urine. This was the first male sex hormone, **androsterone**, $C_{19}H_{30}O_2$. It was found later that the concentration of androsterone in male urine amounts to 1 mg/litre (the very small quantity isolated for the first time is accounted for by the difficulties due to imperfection of the isolation technique). In 1935, Laqueur and David isolated, from steer testes, the male sex hormone **testosterone**, $C_{19}H_{28}O_2$, which is 10 times as potent as androsterone. Androsterone is the reduction product of testosterone.

At an earlier time, in 1929, Butenandt and Doisy independently isolated the first female estrogenic hormone, **estrone**, $C_{18}H_{22}O_2$. It is contained in high concentrations in the urine of pregnant women and females and also in male urine, e.g., in the urine of stallions, from which it is extracted. This is not surprising since the organism gets rid, in this way, of the undesirable hormone. Estrone is one of the series of the physiologically and structurally related estrogenic hormones that have been isolated. These hormones induce the state of estrus (heat) in animals and provide the first phase of the female menstrual cycle. An even more potent estrogen is **estradiol**, $C_{18}H_{24}O_2$, which was isolated from the animal ovaries. An indicator of the action of hormones of this kind is the castrated mouse: the injection of a certain minimal amount of the hormone (1 mouse unit) induces the state of estrus. There is another group of female sex hormones, **hormones of the corpus luteum** (yellow body), which govern the processes of pregnancy. These hormones, which are variously called *progestins*, *corpus luteum hormones*, *pregnancy hormones*, *gestogens*, are produced by the yellow body (yellow tissue) which is formed in the ovaries after ovulation in the first phase of the female menstrual

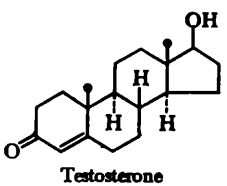
cycle. An example of such hormones is **progesterone**, or **luteosterone**, $C_{21}H_{30}O_2$. The biological function of the gestogenic hormones, represented by progesterone, is to bring about proliferation of the lining of the uterus to prepare it for the implantation of the fertilized ovum (secretory phase). Its prime function is to maintain pregnancy. It is interesting that the estrogenic hormones (or estrogenically functioning substances) are widely distributed in nature. They have been found in flowers and in the fruits of many plants. The estrogens exert a stimulating action on the growth and blossoming of plants. The manure probably owes its useful effect in the fields to the estrogens invariably present in it. At present, these hormones and some of their synthetical physiologically active analogues are employed as valuable medicinal drugs. For example, estrone and testosterone are used as tonics and drugs eliminating the insufficient productivity of the gonads, caused either by a disease or age. In certain cases, they are effective in the treatment of cancer (prostate and thoracic glands, etc.). Progesterone prevents the abortion and provides the normal development of pregnancy. All these hormones are produced in the body under the influence of gonadotropic hormones secreted by the hypophysis (the pituitary) and being of a different nature. The removal of the hypophysis as well as gonads leads to the weakening of the sexual function.

Below are given the formulas of the most important female and male sex hormones:

Androgenic Hormones (Androgens)

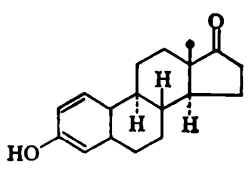


Androsterone

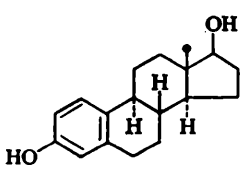


Testosterone

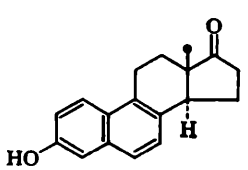
Estrogenic Hormones (Estrogens)



Estrone (folliculin)

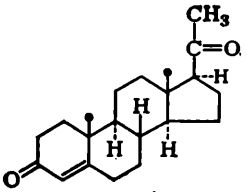


Estradiol



Equilenin

Gestogens (Corpus Luteum Hormones)

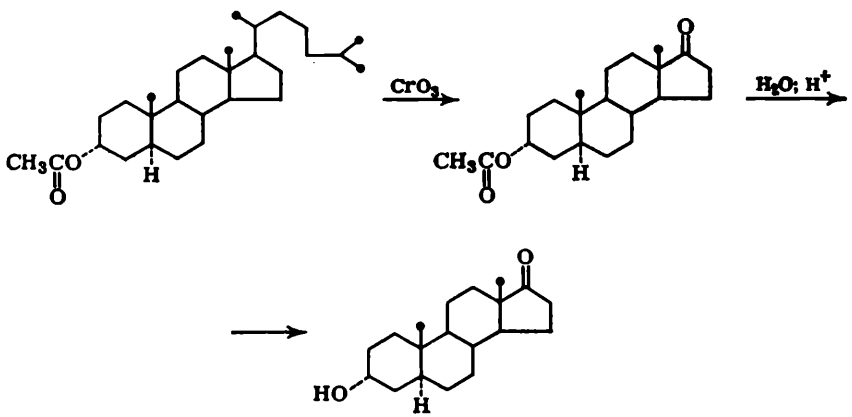


Progesterone (luteosterone)

The carbon skeleton of all these compounds are structurally the same; the estrogens differ in having lacking one angular methyl group, and progesterone has an acetyl side chain at position 17. The rings B/C, and C/D have the *trans*-configuration, as is always the case.

The problem of the *cis*- or *trans*-junction between rings A and B arises only in the case of androsterone. This is a *trans*-linkage, as evidenced by its preparation (Ruzicka; the yield is only 0.5 per cent) through the oxidation of epidihydrocholesterol acetate with chromic trioxide. The rings A and B in epidihydrocholesterol have the *trans*-decalin configuration.

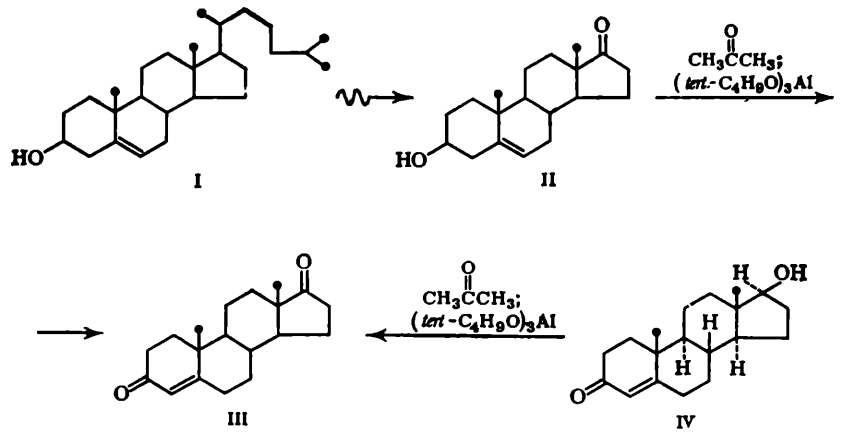
The synthesis of androsterone is as follows:



The same reaction proves that both compounds have the same hydroxyl configuration (the α-hydroxyl group) and differ in this respect from cholesterol (the β-configuration, *cis* to the nearest methyl group). The hydroxyl group of epidihydrocholesterol has the same configuration as that of epiandrosterone, the stereoisomer of androsterone.

The relationship between the structures of androsterone and testosterone is established as follows. Testosterone IV and dehydroepiandrosterone II are oxidized by acetone in the presence of aluminium *tert*-butoxide by the Oppenauer method to the same diketone III

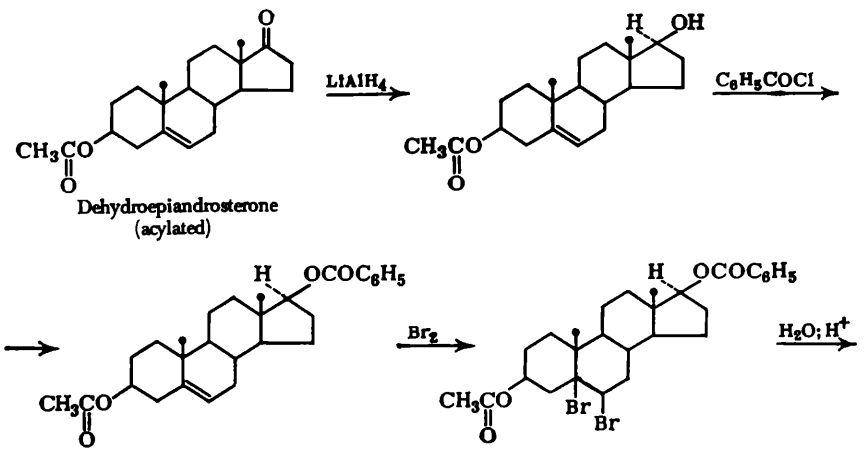
with a conjugated system of bonds, C=C—C=O. Dehydroepiandrosterone II in its turn is prepared by the gradual oxidation of cholesterol I, the double bond of which is protected by addition of bromine which is then eliminated by zinc. This multistage change is expressed in the following scheme by a wavy arrow:

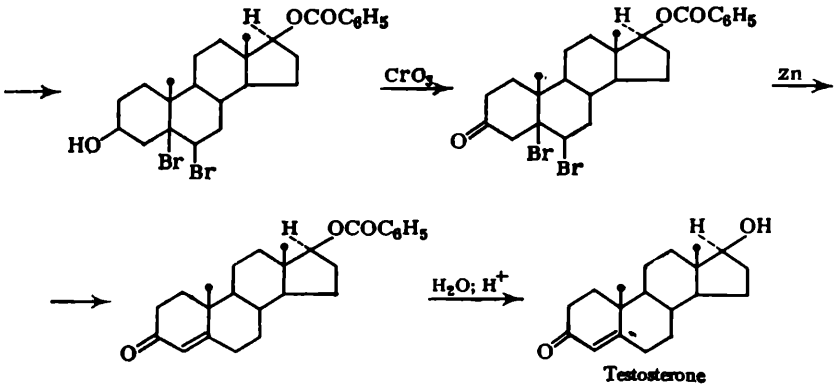


The migration of the double bond to the carbonyl-conjugated position, which is observed in the oxidation of II to III, occurs in many analogous reactions.

Dehydroepiandrosterone serves as a starting point for synthesis of testosterone; the scheme of this synthesis is given below.

Testosterone is prepared from dehydroepiandrosterone by the following series of reactions:



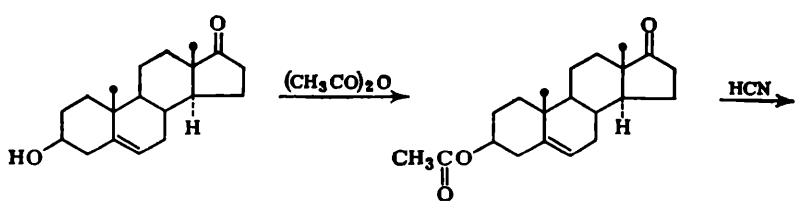


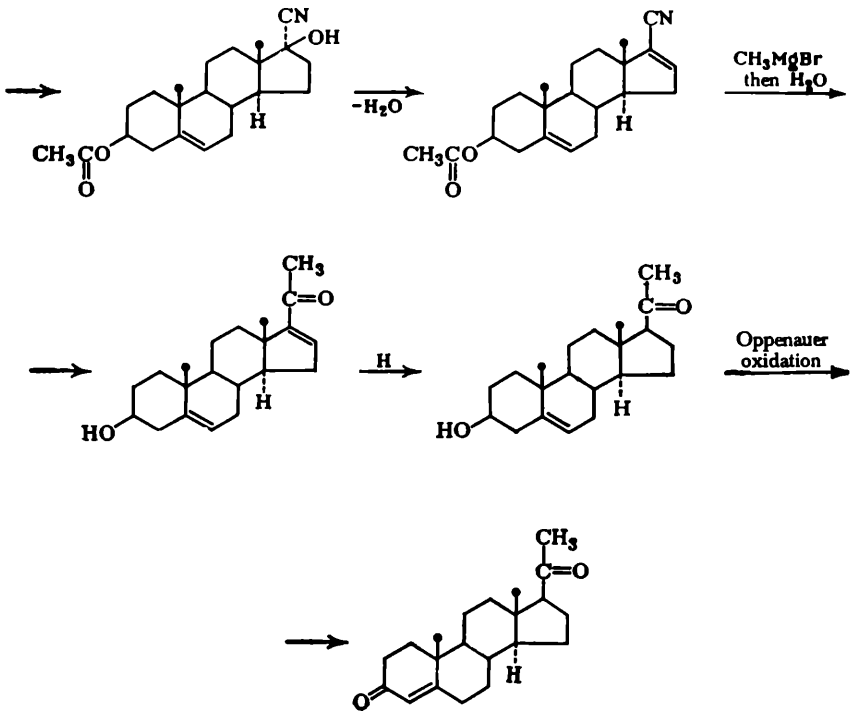
The synthesis is based on the fact that in any reduction reaction the 17-keto group is reduced to a 17-β-hydroxy compound with the configuration corresponding to testosterone. The esters of the 17-hydroxy group are more difficult to hydrolyse than those of the 3-hydroxy group. As always, the double bond from ring B readily migrates to ring A to the position conjugated with C=O.

All estrogenic hormones have a phenol grouping, and equilenin, in particular, has the β-naphthol grouping, which is easily established by ordinary reactions of the aromatic nucleus.

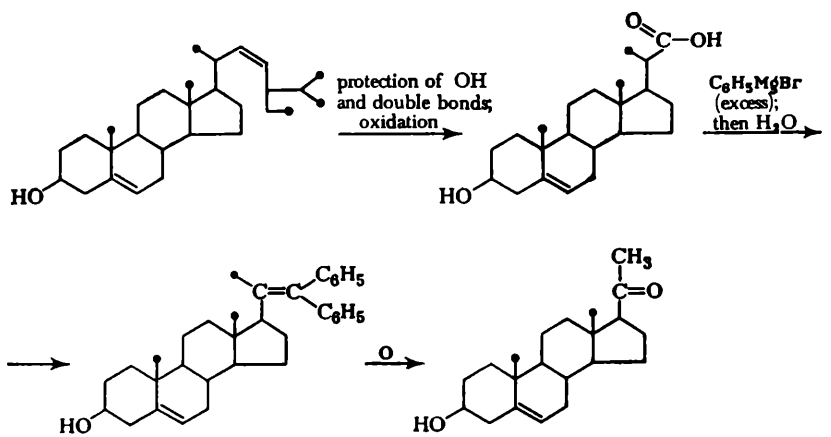
When the keto group of estrone is reduced, two stereoisomeric diols are formed—**estradiol**, $C_{18}H_{24}O_2$, having a more active hydroxyl group with less steric hindrances (hence, the β-hydroxyl group) and its epimer. Estradiol was first prepared in this way from estrone and later from the ovaries of animals. The structure of estrone has been elucidated by the oxidative degradation of the pentane ring and by comparison of the degradation (and dehydrogenation) products with the synthetically produced derivatives of phenanthrene.

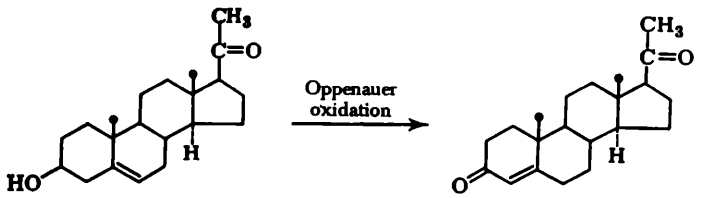
The structure of progesterone has been established by degradation and confirmed by its synthesis from dehydroepiandrosterone. In the production of this medicinally important hormone, use is made of the method devised by Butenandt and co-workers, which is given below.



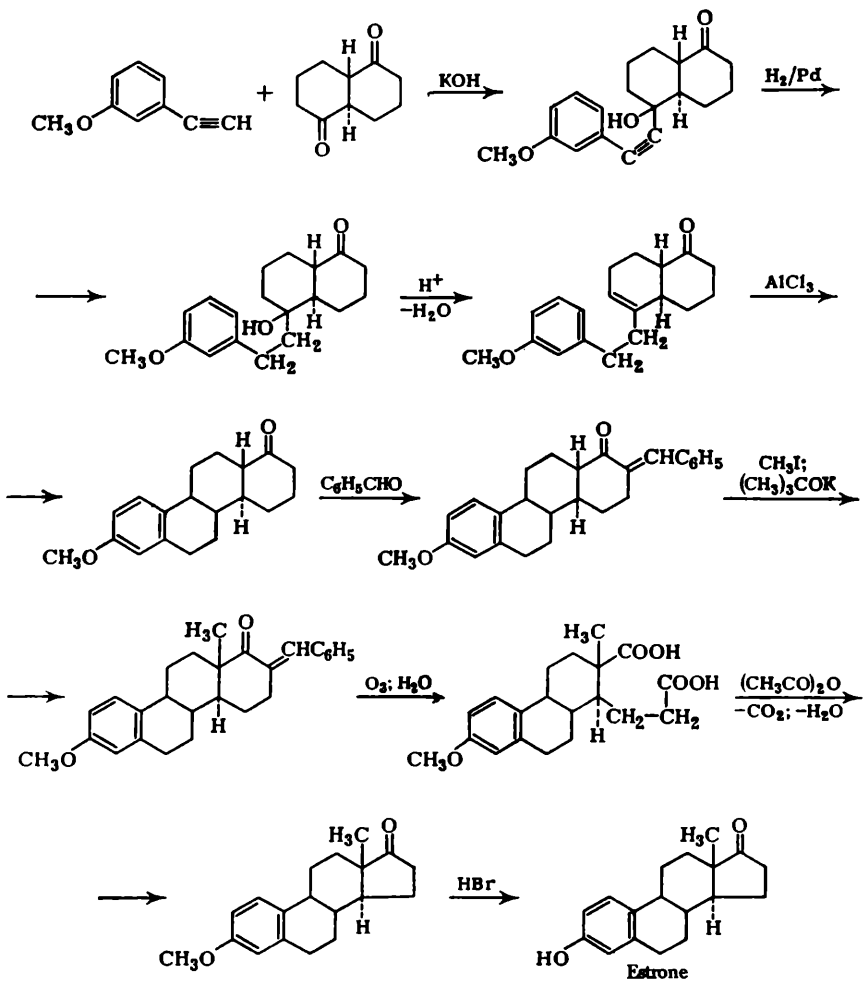


Even simpler is the synthesis of progesterone from stigmasterol (Slotta and Butenandt):

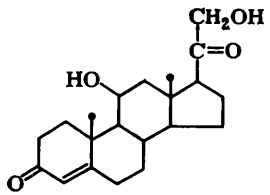




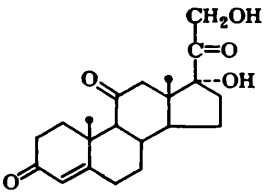
Woodward and Johnson have accomplished total syntheses of all the principal steroidal hormones, which are not given here because they are multistage processes. We shall limit ourselves to a relatively concise total synthesis of estrone according to Johnson:



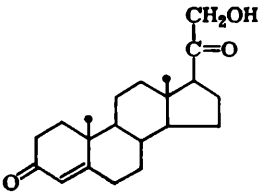
Hormones of the Adrenal Cortex — Corticosteroids. While the medulla of the adrenal glands releases the hormone adrenaline or epinephrine (Volume III, page 193) into the blood stream, the adrenal cortex, a small gland lying near the kidneys, synthesizes and secretes a series of steroid hormones into the blood stream. These adrenocortical hormones are essential to life; without them life would be impossible. The surgical removal of the adrenal cortex is lethal, and its insufficient activity (the hypofunction of the adrenal cortex) causes a disease that, in man, is known as Addison's disease. About 40 individual steroids have been extracted from the adrenal cortex (Reichstein). We shall cite only corticosterone I as the key structure, cortisone II and desoxycorticosterone III:



I



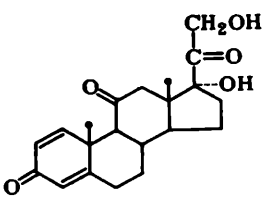
II



III

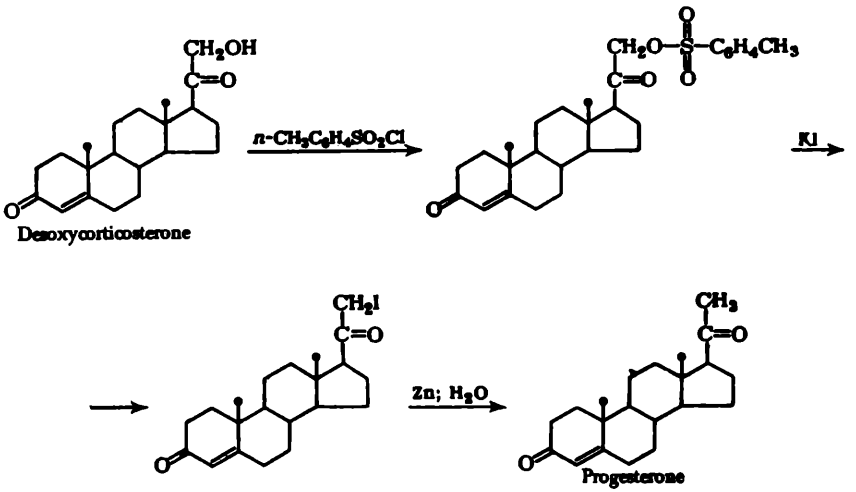
Cortisone performs an important function in the carbohydrate metabolism, namely, in the synthesis of glycogen and in the conversion of proteins into carbohydrates, and participates in the removal of water from the body; evidently, the main function of **desoxycorticosterone** is to maintain the normal salt balance (the K^+:Na^+ ratio) in the body. Of special interest to medicine is cortisone, an important drug used for the treatment of rheumatism and arthritis.

Some purely synthetic steroids have the same effect and are also used in medicine. An example is **prednisone**:



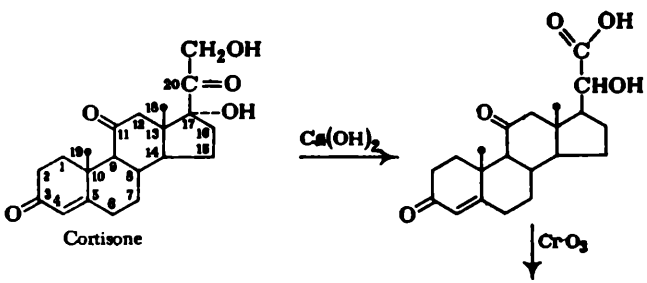
The structurally simplest compound in this group of hormones is **desoxycorticosterone** III, which is 21-hydroxyprogesterone; this has been proved by the replacement of the hydroxyl group in the side

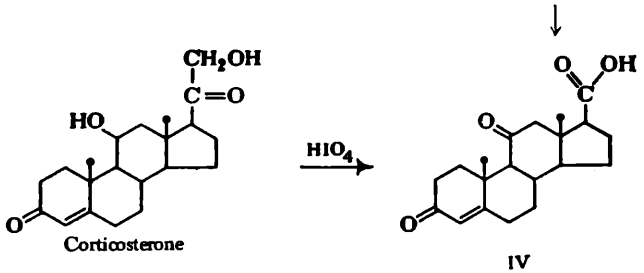
chain by iodine followed by the reduction of the latter with zinc:



All the adrenal cortical hormones have the grouping $-C(=O)-CH_2OH$, and therefore show a number of special properties—they form osazones and give specific oxidation reactions. When they are oxidized with periodic acid, the CH_2OH group is removed in the form of formaldehyde and the carboxyl group is found to have taken the place of $-C(=O)-CH_2OH$.

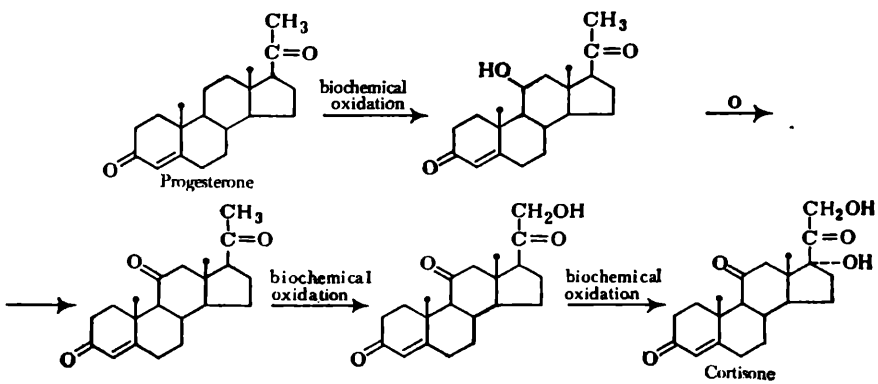
Desoxycorticosterone differs from corticosterone by the lack of one hydroxyl group. Corticosterone and cortisone (after isomerization) on oxidation give the same unsaturated diketonic acid IV, from which it follows that in both compounds the oxygen atom (of the hydroxyl in corticosterone, and of the carbonyl in cortisone) is situated in the same position:





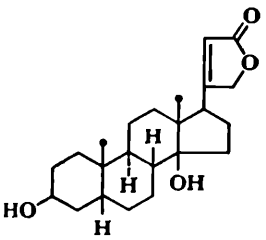
It has been very difficult to establish the position of the unusual hydroxyl group in the ring C of corticosterone and of the carbonyl group in cortisone, the more so that the carbonyl group of cortisone in question is inert and does not give ordinary ketonic derivatives. Since one carbonyl group occupies the position 3, the acetyl and hydroxyl groups are in position 17, and the double bond begins from the fourth carbon atom, there remain the positions 1, 2, 6, 8, 11, 12, 15, and 16 for the third carbonyl group. Cortisone, however, does not exhibit the sufficiently characteristic properties of 1,2- and 1,3-diketones. This rules out the positions 1, 2, 15, and 16. The properties of the carbonyl group in positions 6, 7, and 12 are known from the products of oxidation of bile acids, and they differ from the properties of the carbonyl group of cortisone — the carbonyl groups 6, 7, and 12 give ketonic reactions. Thus, there remains the position 11 for the third carbonyl group of cortisone.

The synthesis of corticosteroids presented great difficulties since the hydroxyl or carbonyl oxygen had to be introduced into position 11, where there is no functional group in all the available starting steroids. After the discovery of the fact that microorganisms are capable of inducing such oxidation reactions and also the fact that by effecting oxidation with yeasts, actinomycetes and the various bacteria, it is possible to introduce the hydroxyl group as desired into the positions 6, 7, 8, 9, 11, 14 15, 16, 17, and 21, and into the α- or β-configurations, it became possible to produce cortisone relatively simply from progesterone:

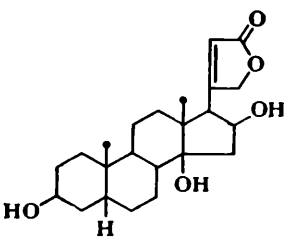


E. Genins and Saponins

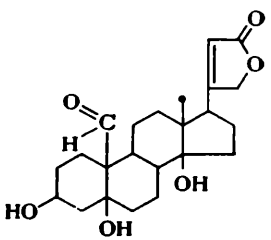
The various species of *Digitalis* (foxglove) and *Strophanthus* contain the glycosides of steroid alcohols, which have long been used in medicine in the treatment of cardiovascular disease. They are highly poisonous compounds. The hydrolysis of these compounds often leads to the separation of the carbohydrate moiety of the molecules from the aglycones known as **genins.** We shall only give the formulas of the most principal aglycones thus obtained—**digitoxigenin** I, **gitoxigenin** II, and **strophanthidin** III:



I



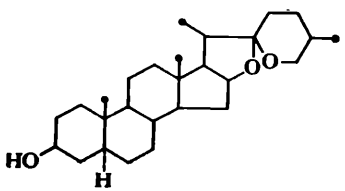
II



III

These and other genins have been obtained by Stoll, Tschesche, and Reichstein. The specific feature of their configuration, which differentiates these compounds from all the types of steroids described earlier is the *cis*-union of rings C and D. The rings A and B have the *cis*-decalin configuration and only rings B and C are joined by the *trans*-linkage.

Widely distributed in plants are **saponins** (e.g., in soapwort). These are poisonous glycosides with strongly pronounced surface activity; like soap, they have the property of forming colloidal solutions with water which foam on being shaken. Their aglycons are called **sapogenins** and belong to the class of steroids. An example is **tigogenin**:



Chapter 22

Alkaloids of the Heterocyclic Series

The alkaloids constitute a group of compounds which, like terpenes, are collected into one class not only according to their chemical behaviour. The alkaloids are now generally defined as basic nitrogen-containing compounds of vegetable origin (some physiologically active basic compounds contained in the animal organism are sometimes also included in this definition), which exert powerful physiological effects on human beings and animals, principally on the nervous system. The basic character and salt-forming ability made it possible, as early as the beginning of last century, to isolate and characterize a large number of alkaloids (morphine, Sertürner, 1806; quinine and colchicine, Pelletier and Caventou, 1820; nicotine, Bosselt and Reimann, 1828; atropine, Mein, 1831; theobromine, A. A. Voskresensky, 1842).

Owing to their strong physiological effect the alkaloids are of great value in medicine, and many of the alkaloids had been utilized, long before they were identified, for curative purposes in the form of plant tinctures and extracts. Even earlier the juices of alkaloid-bearing plants had been used as arrow poisons, say, those containing curare and strychnine.

The alkaloids, along with physiologically active glycosides, have long become an essential part of the arsenal of medicine and the number has been increasing due to new discoveries. Many important alkaloids of complex structure have been isolated in the individual state relatively long ago but their structures have been elucidated in this century, some of them only recently, and the syntheses of the most complicated of them (quinine, strychnine, reserpine) have been effected in recent years.

The alkaloid-bearing plants are largely plants belonging to a few families: papilionaceous, leguminous, poppy, nightshade, crawfoot, madder, and *Compositae* families. Generally, the alkaloids are concentrated not in all but in certain definite tissues of the plant

(nicotine is present in the leaves of tobacco, quinine in the bark of the cinchona tree, etc.). Often a single species of the plant contains several alkaloids. The alkaloids are associated in plants into salts, which are formed either by the widely distributed acids of the plant kingdom—malic, tartaric, citric, etc., or, in certain cases, by acids specific for a given alkaloid. Alkaloids are isolated by treating the alkaloid-containing tissue with alkali or ammonia, then the free alkaloid is extracted from the aqueous solution by ether, chloroform or other organic solvent, following which the alkaloid is passed again into the aqueous acid solution. Use is often made of the fact that many alkaloids form slightly soluble salts with picric and phosphotungstic acids and are precipitated with tannin and the anion HgI_3^-. For a mixture of alkaloids to be separated, use is made of the solvent extraction technique at various pH or chromatography.

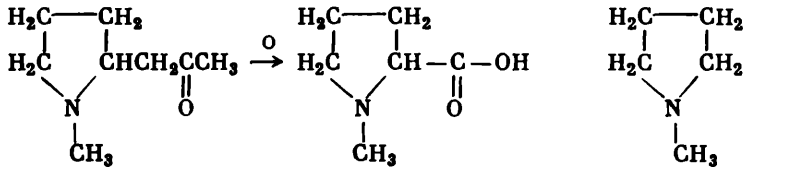
At present about 1000 alkaloids are known, but the structures of a considerable number of these alkaloids have not yet been established. Most of them have been discovered in this century. Major contributions to the investigation of alkaloids have been made by the following scientists: G. Barger, R. Robinson, H. Wieland, R. Willstätter, E. Späth, R.H.F. Manske, D.H.R. Barton, P. Karrer, V. Prelog, R. B. Woodward, A. P. Orekhov and his school (G. P. Menshikov, R. A. Konovalova, N. F. Proskurina, S. Yu. Yunusov, A. S. Sadykov), A. E. Chichibabin and his pupils (N. A. Preobrazhensky, M. N. Shchukina).

The alkaloids are classified according to their nitrogen-carbon skeleton. A few alkaloids of the aliphatic and aromatic series, containing nitrogen in the side chain (ephedrine, colchicine) have already been considered (see Volume III, page 194, and page 163 in this volume) and will not be discussed here. The heterocyclic alkaloids may be divided into the groups that follow.

22.1. Alkaloids with a Five-Membered Heterocycle Containing One Nitrogen Atom

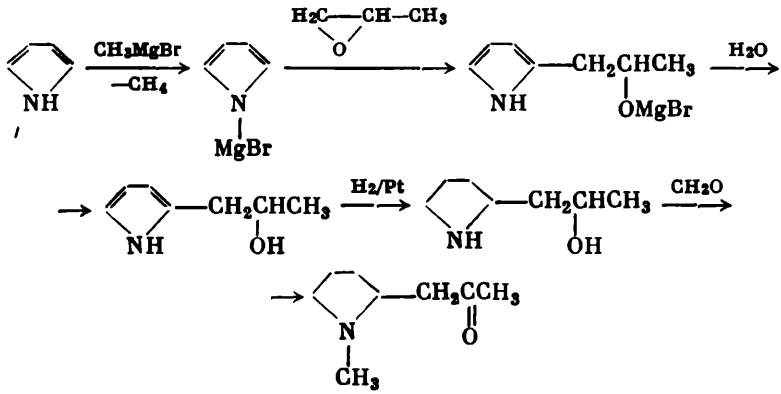
One of the structurally simplest alkaloids is **hygrine**, $C_8H_{15}NO$, which was isolated from the leaves of South American coca (Wöhler, Lossen, 1862), and later from one of the bindweed species (L. V. Lazurevsky, 1939). This is a ketone which on oxidation forms N-methylproline (page 406), which proves its close structural relationship

to N-methylpyrrolidine:



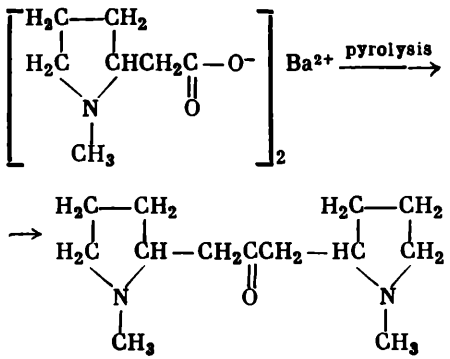
Hygrine | N-Methylproline (hygrinic acid) | N-Methylpyrrolidine

The synthesis of hygrine has been accomplished by the following scheme:



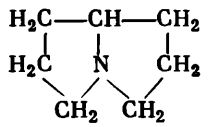
At the last stage, the nitrogen is methylated by the action of formaldehyde and the secondary alcoholic group is simultaneously oxidized to a carbonyl group (this reaction is due to K. Hess).

Structurally related to hygrine is **cuskohygrine** (or *cuscohygrine*), $C_{13}H_{24}N_2O$, which is present in the crude hygrine obtained from cusko leaves. The synthesis of cuskohygrine proves its structure. It was synthesized by G. V. Lazurevsky:

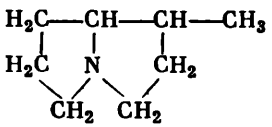


22.2. Alkaloids with a System of Two Condensed Five-Membered Rings Containing One Common Nitrogen Atom

A large group of alkaloids, which are found in some of the Compositae (groundsel) and other plants, have, as its basic unit, the bicyclic structure of pyrrolisidine, namely, 1-methylpyrrolisidine, known as heliotridane.

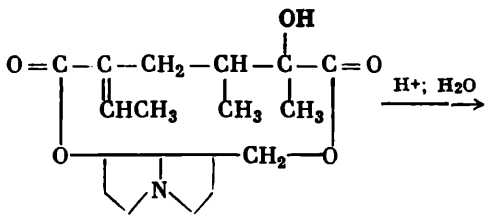


Pyrrolisidine

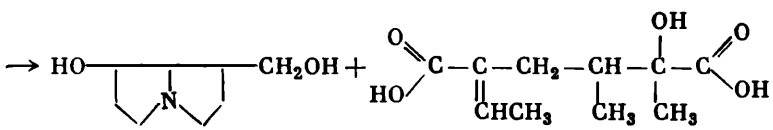


Heliotridane

Of great therapeutic importance is **platiphyllin**, an ester which on hydrolysis decomposes into the two-hydroxyl heterocyclic alcohol **platinecine** and **senecionic acid**. Platiphyllin is used as a vasidilator and antispasmodic (A. P. Orekhov).



Platiphyllin*



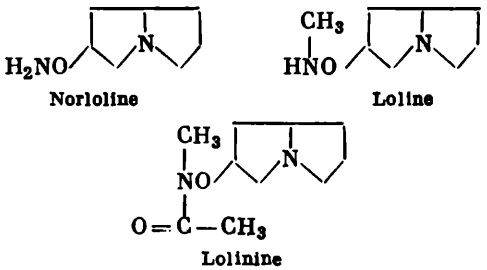
Platinecine

Senecionic acid

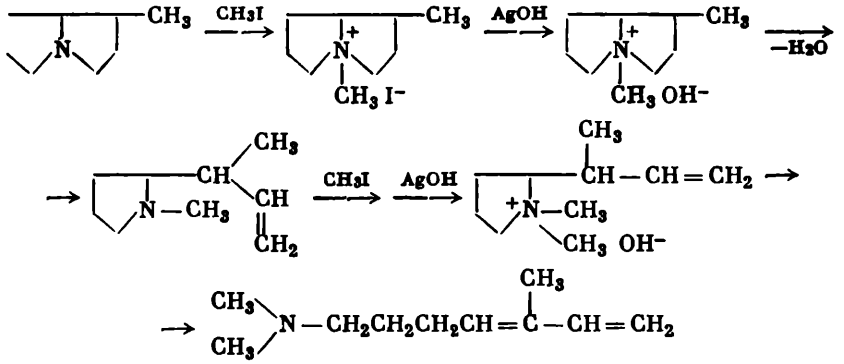
The investigation of the structure of numerous alkaloids of this group has been carried out by Orekhov's school—G. P. Menshikov, S. Yu. Yunusov *et al.* Thus, Yunusov has elucidated the structure of a number of alkaloids with the pyrrolisidine ring, of which the

* The possibility is not excluded that senecionic acid esterifies platinecine in a different order and that its residue should be turned 180° in the formula of platiphyllin given.

following three alkaloids are given:



Menshikov has also established the structure of the basic heterocyclic ring of these alkaloids, heliotridane (1-methylpyrrolisidine), by the Hofmann degradation:

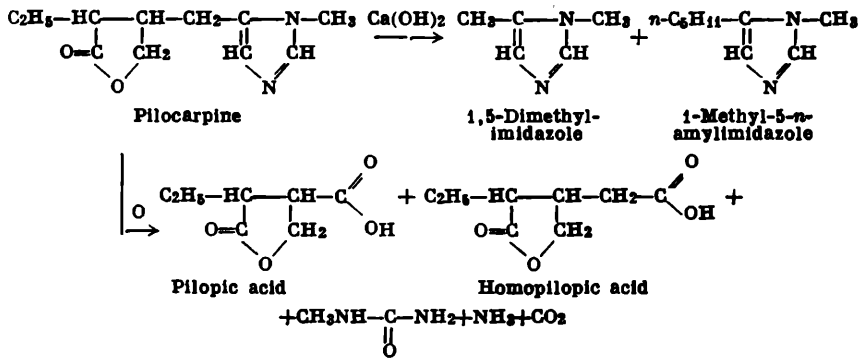


22.3. Alkaloids with a Five-Membered Heterocycle Containing Two Nitrogen Atoms

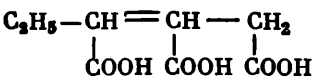
Pilocarpine was isolated (Ardis, 1895) from the leaves of *Pilocarpus jaborandi* which grows in Africa and has found wide application in the treatment of glaucoma—the eye disease associated with the increased intraocular pressure, which is the cause of blindness in the majority of cases. Pilocarpine, in contrast to atropine, contracts the pupil of the eye.

The structure of pilocarpine as a derivative of imidazole (glyoxaline) follows from its conversion on heating with lime into 1,5-dimethylimidazole and 1-methyl-5-*n*-amylimidazole. On the other hand, when pilocarpine is oxidized with permanganate, along with the nitrogen-containing decomposition products of the imidazole

ring, there have been obtained pilopic acid and its homologue, homopilopic acid:

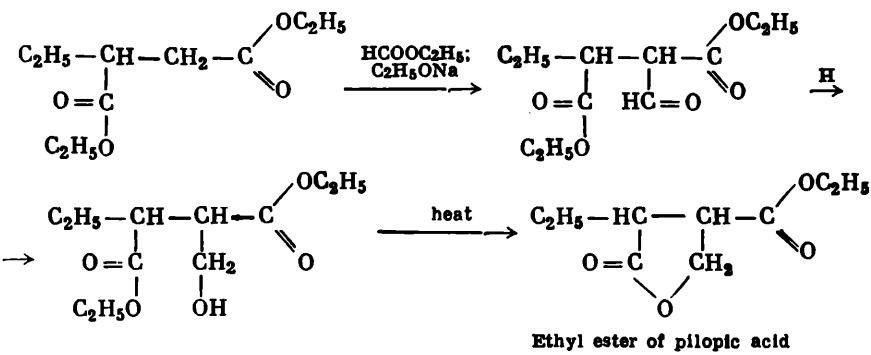


When reacted with alkali under vigorous conditions, homopilopic acid forms pentane-1,2,3-tricarboxylic acid

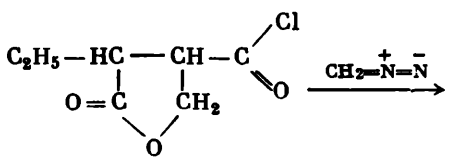


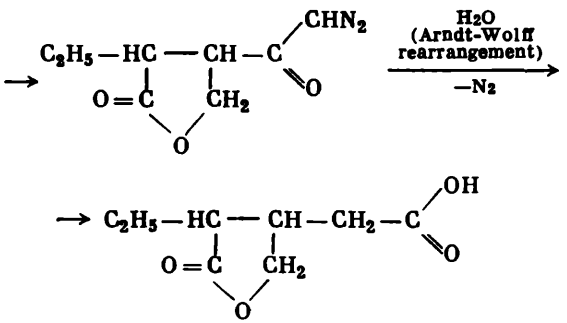
and, hence, is a lactone acid.

The structure of pilopic acid has been confirmed by synthesis (A. E. Chichibabin and N. A. Preobrazhensky):

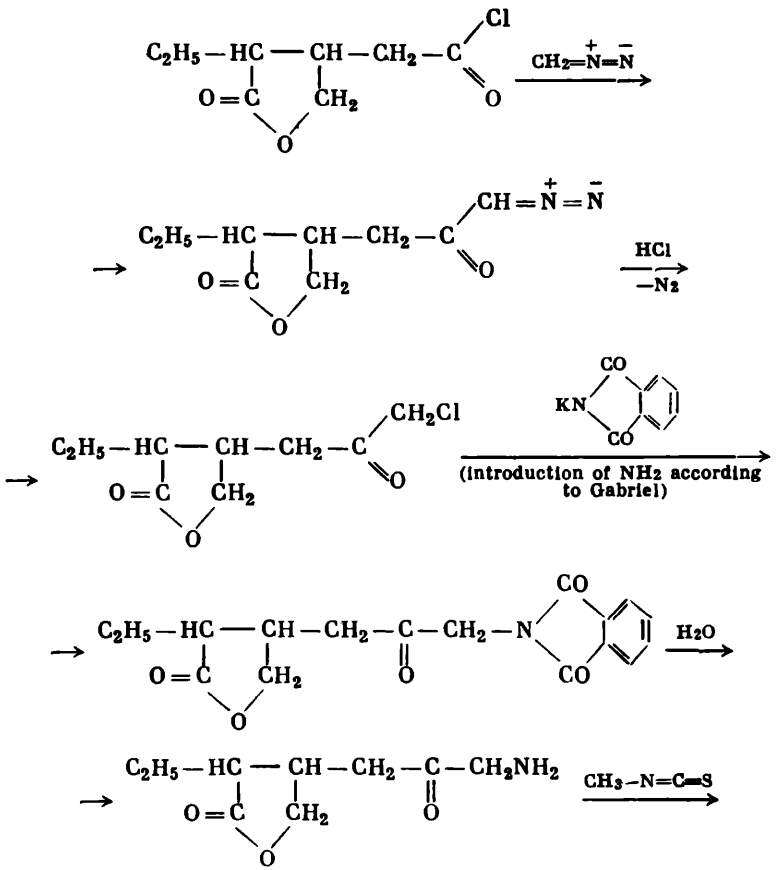


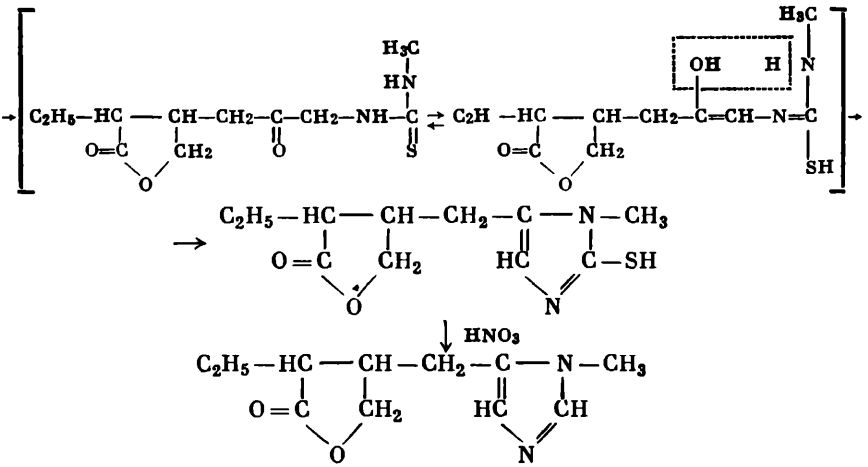
Pilopic acid can be converted, by means of the Arndt-Wolff reaction, into homopilopic acid, which establishes their relationship:





The synthesis of pilocarpine has been accomplished by N. A. Preobrazhensky and his co-workers, starting from the acid chloride of homopilopic acid:

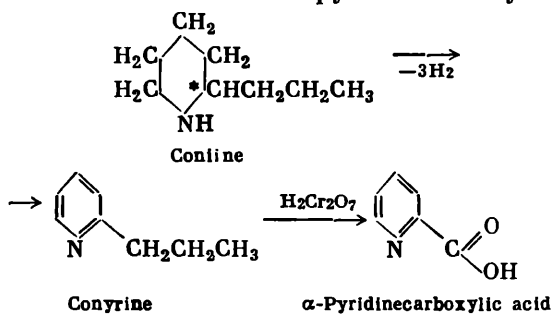




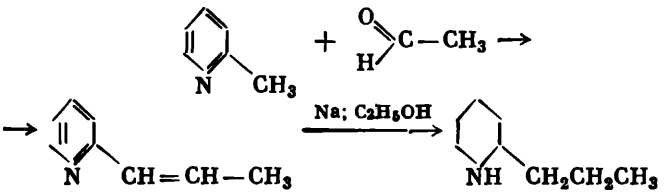
Enclosed in square brackets are the intermediates which are not isolated. Methyl isothiocyanate adds on to the amino group, just as in the familiar reaction of addition of isocyanates (see, for example, the Traube synthesis of derivatives of uric acid and other substituted purines). The tautomeric form of the resulting derivative of thiourea undergoes cyclization with elimination of water.

22.4. Alkaloids with a Six-Membered Heterocycle Containing One Nitrogen Atom

The basic structural unit of a large group of alkaloids is the piperidine ring. Piperidine itself is also found in one of the plants of the madder family. **Coniine** (the principal alkaloid of hemlock, *Conium maculatum*, a potent poison) is α-propylpiperidine, which follows from its dehydrogenation to α-propylpyridine, or **conyrine**, and the oxidation of the latter to α-pyridinecarboxylic acid:



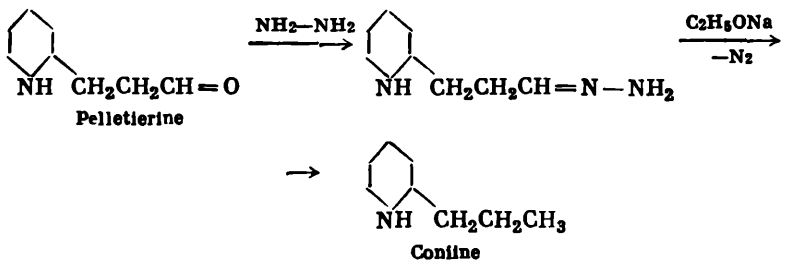
Ladenburg synthesized coniine in the following way:



and resolved the resulting racemic product into the antipodes by crystallizing its salt with D-tartaric acid. The dextrorotatory isomer is identical with the natural compound.

A number of alkaloids are found to accompany coniine in the plant hemlock. These are the oxygen derivatives of coniine: the secondary alcohols **conhydrine** (the hydroxyl group is present in the side chain) and **pseudoconhydrine** (the hydroxyl group is in position 5 of the piperidine ring).

Among other alkaloids, the root of the pomegranate contains **pelletierine**, an aldehyde which can be converted, by the Kishner reduction, into coniine, which proves its structure:

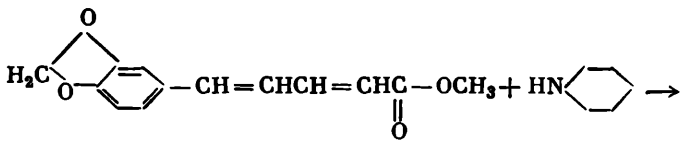


Pelletierine

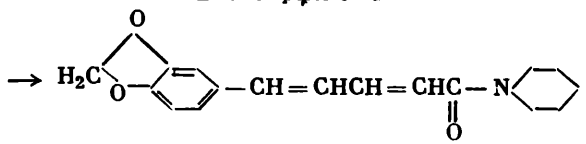
Coniine

Pelletierine is used as an anthelmintic.

Piperine, $C_{17}H_{19}O_3N$, is an alkaloid present in pepper, especially black pepper (*Piper nigrum*). The hydrolysis of piperine gives piperidine and piperic acid. It can be prepared by the acylation of piperidine by this acid:



Ester of piperic acid

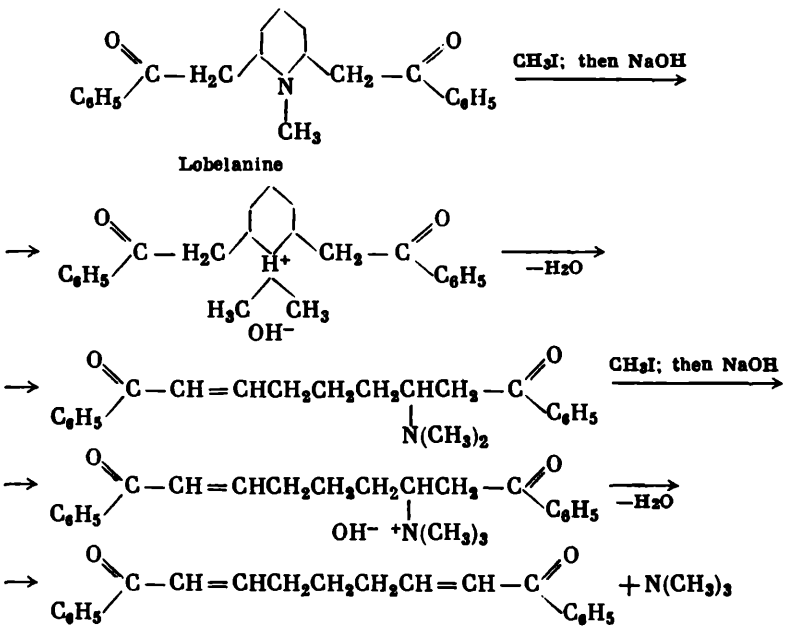


Piperine

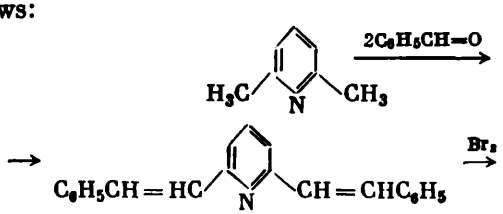
The established structure of piperic acid is the one given above (on oxidation it gives the aldehyde piperonal, or heliotropin).

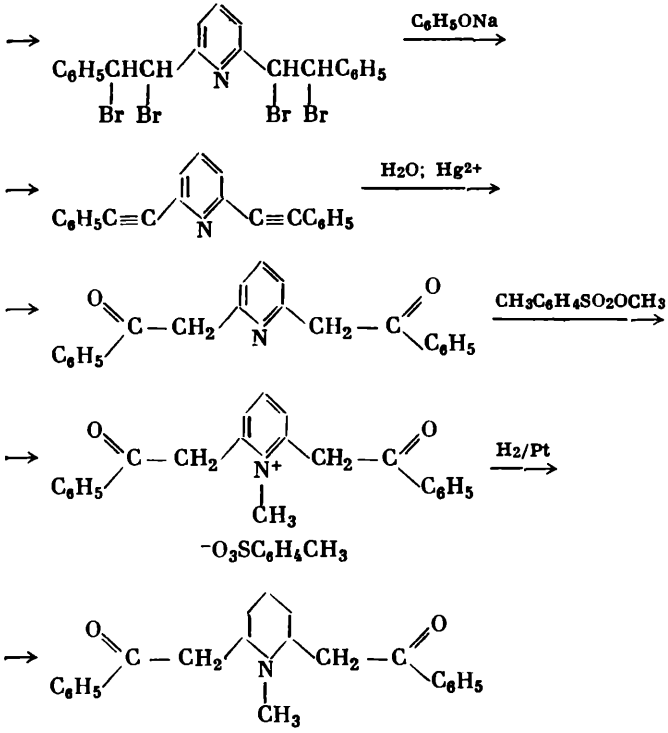
The most important of the many alkaloids present in the seeds of *Lobelia inflata* is **lobeline**, which is used in medicine to stimulate the respiratory centres of the brain (it is an excellent cardiac stimulant). This is a tertiary amine and also a ketone and a secondary alcohol; when oxidized it is converted into the diketone **lobelanine**, which on heating with zinc dust forms such an amount of acetophenone that the presence of two $C_6H_5CCH_2-$ groups becomes clear.
$$\|$$
$$O$$

The Hofmann degradation of lobelanine leads to 1,7-dibenzoylheptadiene:



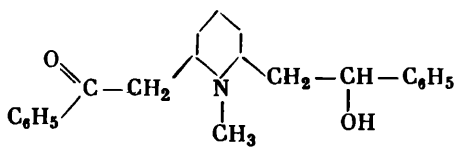
With two $C_6H_5COCH_2-$ groups being removed, there remain five carbon atoms which were closed together with one nitrogen atom into the piperidine ring. The synthesis of lobelanine was accomplished as follows:





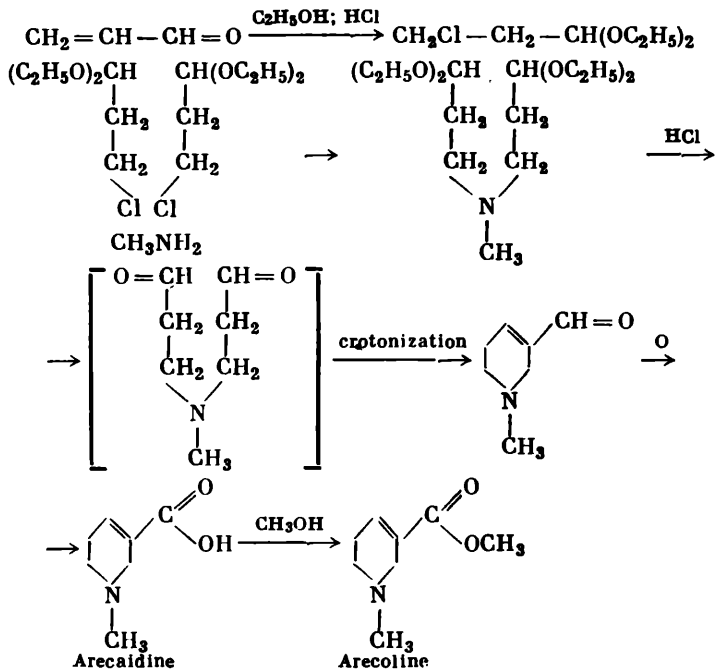
Lobelanine

The reduction of one of the keto groups of lobelanine leads to the above-mentioned alkaloid lobeline



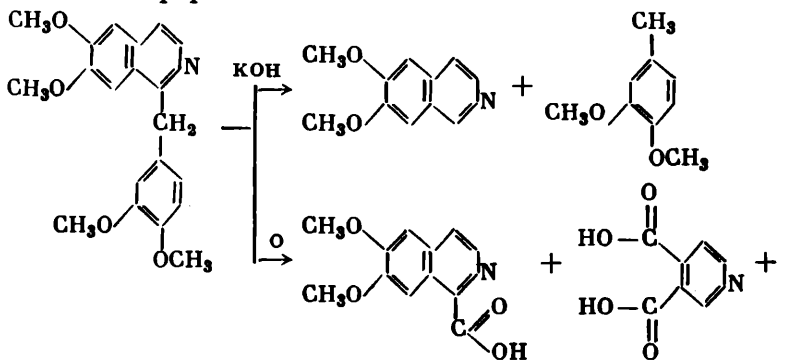
Lobeline

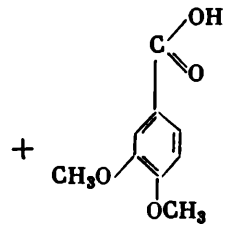
The seeds of the betel nut (*Areca catechu*) have been found to contain a group of related alkaloids. Of these we shall consider only **arecoline** and **arecaidine** (the latter is an acid and the former is its methyl ester). Arecoline is used in veterinary and medicinal practice. Both are cyclic tertiary amines containing one double bond in the ring. The hydrogenation of arecaidine yields N-methylpiperidine-β-carboxylic acid. The synthesis of arecaidine establishes the position of the double bond:



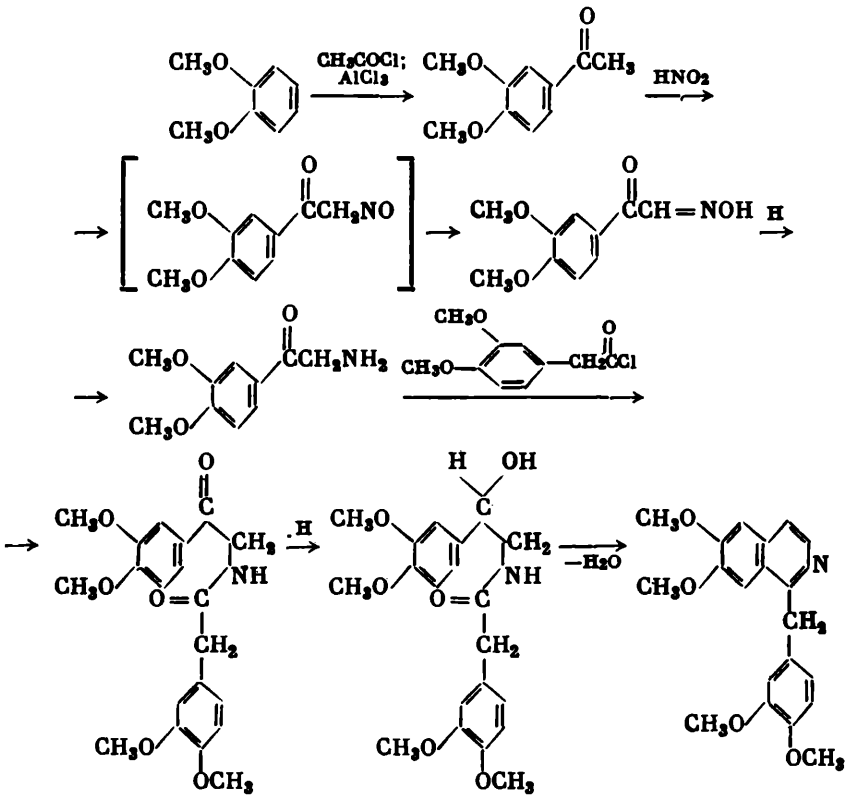
The seeds of the opium poppy contain the alkaloid **papaverine**, $C_{20}H_{21}O_4N$, the structure of which was established by G. Goldschmiedt. The synthesis of papaverine was effected by Pictet in 1909. Papaverine is extensively used in medicine as a vasodilator (e.g., in hypertension).

As shown by analysis, the papaverine molecule contains one nitrogen atom and four methoxy groups. The degradation of papaverine (fusion with alkali and oxidation) yields the dimethoxy derivatives of isoquinoline and toluene or benzoic acid, from which follows the structure of papaverine:





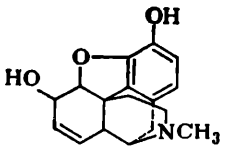
The synthesis of papaverine first accomplished by Pictet and Gams is as follows:



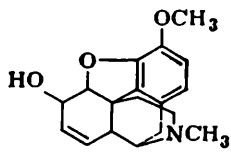
The juice of the unripe poppy seeds contains the closely related (structurally) opium alkaloids **morphine** and **codeine**. The two alkaloids have a tertiary nitrogen atom bearing a methyl group and three oxygen atoms each—a secondary alcoholic oxygen (oxidation to a ketone), ether oxygen, and a phenolic oxygen (in morphine) and a methylated phenolic oxygen (in codeine). Morphine when methylated in alkaline medium is converted into codeine. Thus, codeine is

the methyl ether of morphine as a phenol. On distillation with zinc dust the alkaloids morphine and codeine form phenanthrene.

Based on the work of many chemists, R. Robinson conclusively established the formulas of these alkaloids:

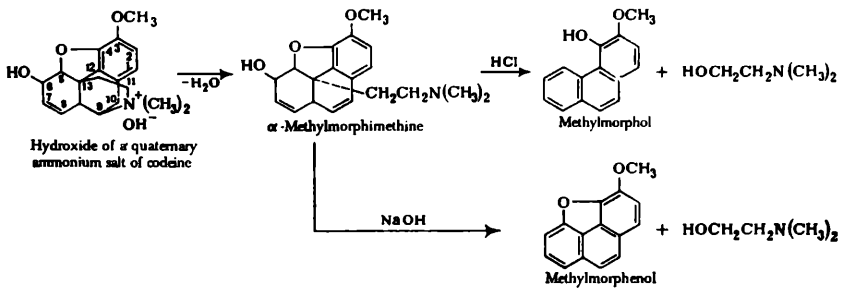


Morphine



Codeine

The Hofmann degradation of codeine converts it into the so-called *α-methylmorphimethine* which is readily cleaved by hydrochloric acid. When α-methylmorphimethine is reacted with alkali, the same chain containing a nitrogen atom is split off, as a result of which the methyl ether of morphenol, methylmorphol, is formed:



Hydroxide of a quaternary ammonium salt of codeine

α-Methylmorphimethine

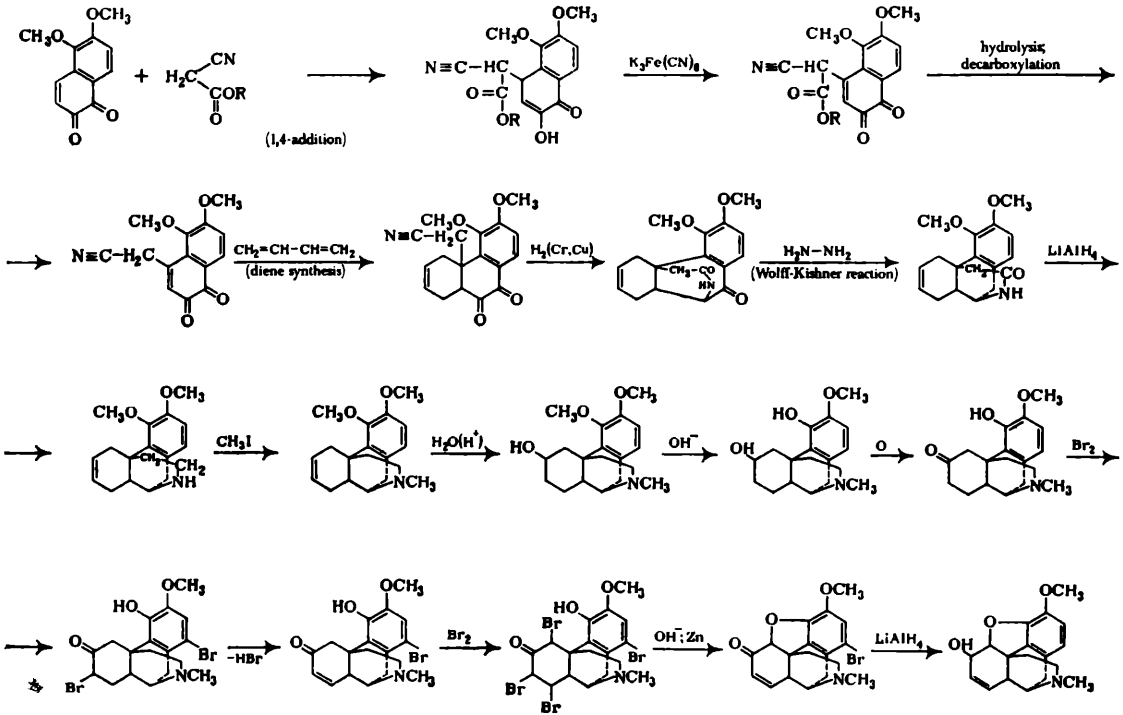
Methylmorphol

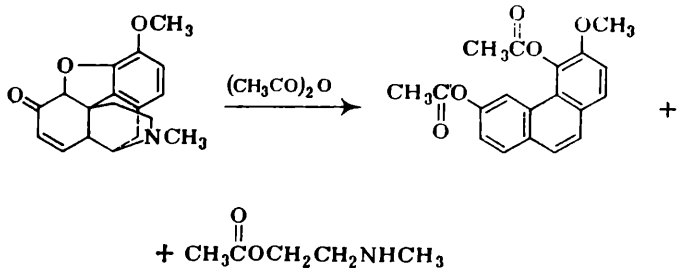
Methylmorphenol

The unusual ease of the cleavage of the C—C bond with elimination of dimethylaminoethanol is accounted for by the fact that the reaction is accompanied by the aromatization of the phenanthrene ring and, hence, by a large energy gain.

Methylmorphol and methylmorphenol are readily obtained by the Pschorr synthesis (Volume III, page 299), and in this way the positions of the oxygen bridge and the methoxyl group in codeine (and, hence, of the oxygen bridge and phenolic hydroxyl group in morphine) are established. A similar elimination of the methylaminoethanol grouping and aromatization of the phenanthrene ring take place on prolonged heating of the ketone codeinone (the oxidation product of codeine as a secondary alcohol) with acetic anhydride. This gives 3-methoxy-4,6-diacetoxyphenanthrene as a phenanthrene derivative, which indicates that the third oxygen atom of codeine (and of morphine) is situated in position 6 (see page 371):

Synthesis of Morphine





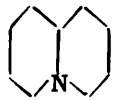
The ease of detachment of the group $HOCH_2CH_2NHCH_3$ in this case and of the group $HOCH_2CH_2N(CH_3)_2$ in the previous case, followed by the aromatization to phenanthrene indicates that this grouping was attached to a quaternary cyclic carbon and the probability of this carbon being incorporated into the six-membered isoquinoline ring leads to the formula proposed by Robinson for morphine. This structure was established in 1927 about 120 years after the discovery of morphine by the apothecary Sertürner (1806)—it was the first alkaloid to be isolated from a plant source. This structure of morphine was confirmed by its synthesis (Gates, 1952) according to the scheme given on page 370.

Morphine is among the most valuable drugs for the relief of pain (an analgesic), but the disadvantage of its use is that it is habit-forming (morphinism). The diacetate of morphine is called diamorphine or **heroin.**

22.5. Alkaloids with a System of Two Condensed Six-Membered Rings Containing One Common Nitrogen Atom

The alkaloid of the seed of certain species of lupin (e.g., *Lupinus luteus* and *Lupinus niger*) called **lupinine**, $C_{10}H_{19}ON$, was discovered by Siewert in 1865. It was also found in the leafless echinocloa growing in Soviet Central Asia by A. P. Orekhov and G. P. Menshikov. It is a tertiary base containing one nitrogen atom which bears the primary alcoholic function. The primary alcoholic group can be oxidized to the aldehyde group and further to the carboxyl group. The decarboxylation of this **lupininic acid** leads to **norlupinine**

which is identical with quinolisidine.

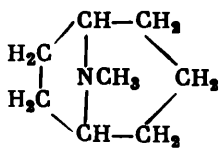


Norlupinine

The Hofmann degradation of lupinine points to the key position of nitrogen in the bicyclic compound and the position of the primary alcoholic group, which proves the structure of lupinine. Each time after methylation with methyl iodide, replacement of the iodide ion by the OH^- ion and pyrolysis with the cleavage of the C—N bond the newly formed C=C bond is hydrogenated and the Hofmann degradation is repeated. This procedure has to be repeated three times in order to bring about the cleavage of the last C—N bond and to eliminate the nitrogen atom in the form of trimethylamine. This proves that the nitrogen atom was linked by three bonds in the rings, i.e., was in the nodal position of the bicyclic compound (see page 373).

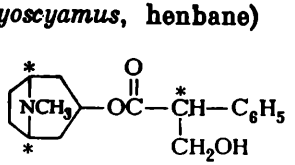
22.6. Alkaloids with Condensed Five- and Six-Membered Heterocycles and One Nitrogen Atom

The Tropane Group. This group of alkaloids which are important therapeutically includes atropine (and hyoscyamine) and cocaine. The principal structural unit of these alkaloids is the heterocycle **tropane**

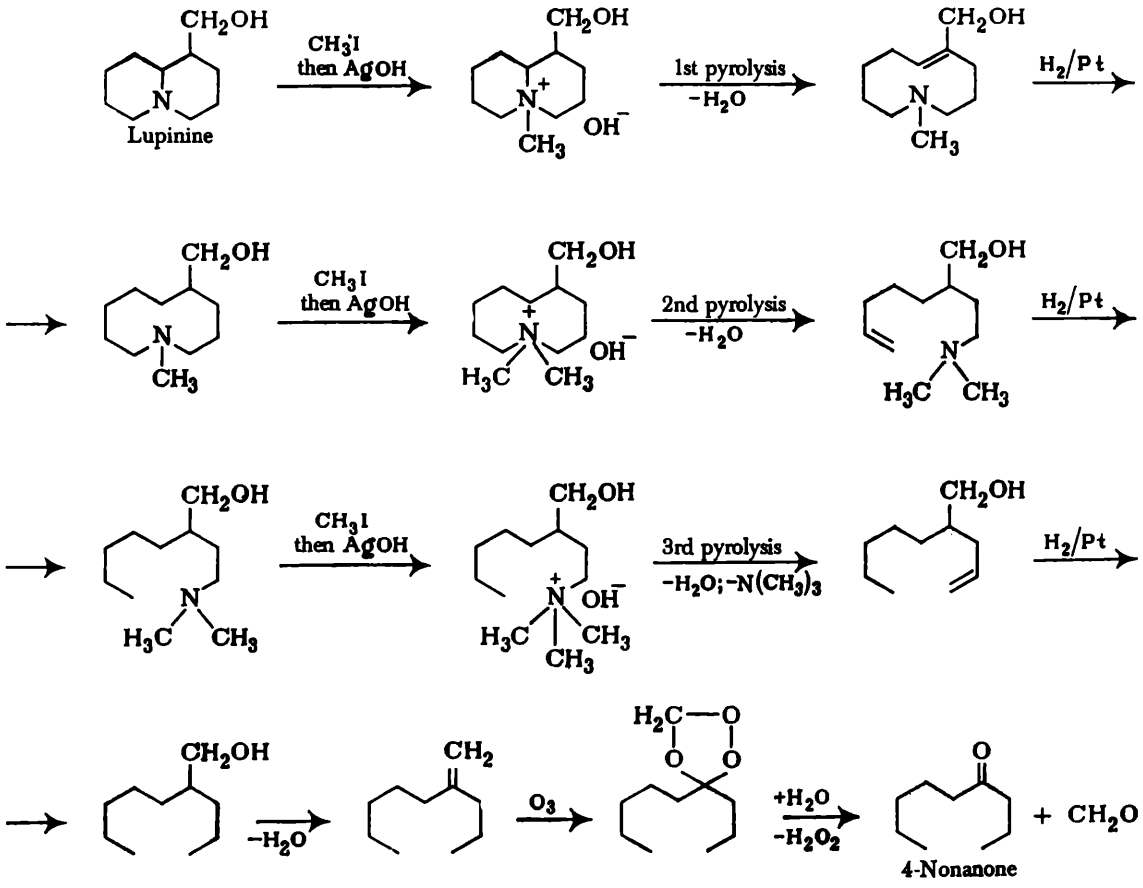


which is a combination of methylpyrrolidine and methylpiperidine, which have two α-CH groups and one NCH_3 group in common.

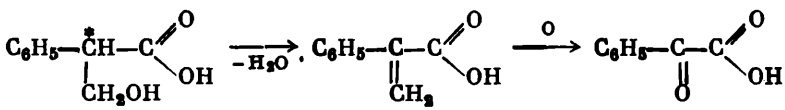
Atropine (from *Atropa belladonna*, "deadly nightshade") and hyoscyamine (from *Hyoscyamus*, henbane)



are stereoisomers and undergo hydrolysis with the formation of the same heterocyclic alcohol tropine and tropic acid (which is optically

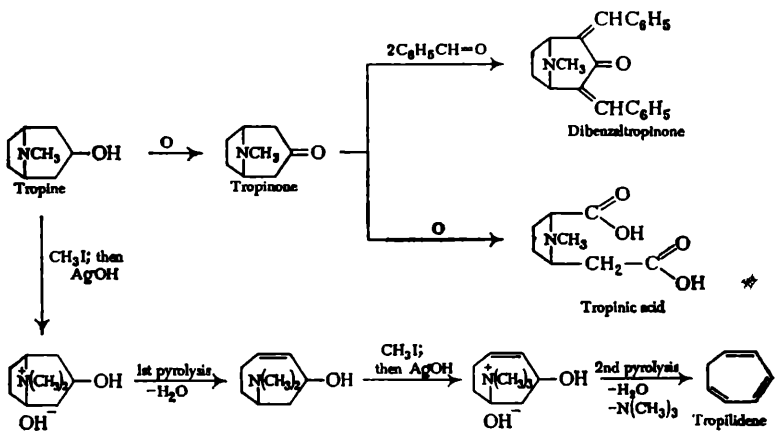

CH2OH
CH3I
then AgOH
Lupinine
OH−
CH3
1st pyrolysis
−H2O
H2/Pt
2nd pyrolysis
H3C
3rd pyrolysis
−H2O; −N(CH3)3
−H2O
CH2
O3
H2C—O
+H2O
−H2O2
O
+ CH2O
4-Nonanone

active for hyoscyamine and racemic for atropine). **Tropic acid** has the structure of α-methylolphenylacetic acid, which follows from its conversion on dehydration to **atropic acid** which is oxidized to benzoylformic acid:

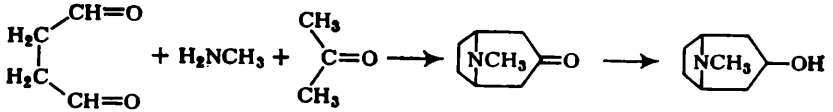


The alcohol **tropine** is oxidized to the ketone **tropinone**, from which it follows that it is a secondary alcohol. Tropinone, like acetone, reacts with two molecules of benzaldehyde, forming dibenzaltropinone, which points to the presence in it of the grouping $-CH_2-$ $-\overset{\overset{O}{\|}}{C}-CH_2-$. This grouping is symmetrical with respect to the remaining nitrogen-containing part of the molecule since the oxidation of tropinone yields only one (Popov's rule) dicarboxylic acid—**tropinic acid**, $C_8H_{13}O_4N$.

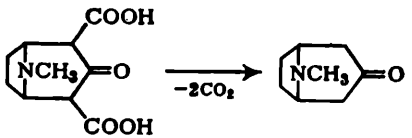
The Hofmann degradation of tropine proves the presence of the bridging NCH_3 group in the biheterocyclic system which contains the isocyclic skeleton of seven carbon atoms. Indeed, for the nitrogen atom to be removed, it is required that methylation and pyrolysis of the hydroxide of a quaternary ammonium base be repeated twice, in which case trimethylamine is eliminated and tropilidene (cycloheptatriene, see Volume II, page 263) is left. All these facts suggest the formula given below for tropine and the following scheme of its conversions:



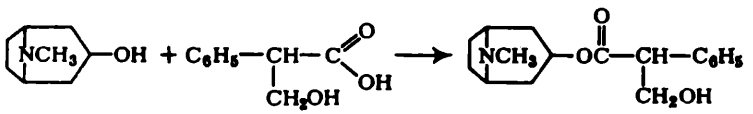
Robinson synthesized tropine, using an elegant method: succinic dialdehyde in the presence of methylamine enters into a croton-type condensation with acetone and methylamine adds across the newly formed double bonds. This gives rise to tropinone which is reduced to tropine:



Acetonedicarboxylic acid may be used instead of acetone. In this case, tropinonedicarboxylic acid is obtained, which, being a β-ketonic acid, is further readily decarboxylated:

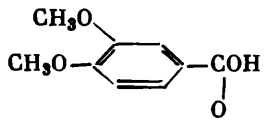


The esterification of tropine with racemic tropic acid affords atropine:



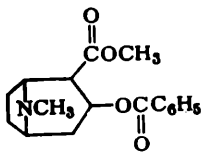
Atropine is an important drug used to relieve spasm (an antispasmodic). Owing to its property of dilating the pupil of the eye (mydriasis) it is extensively employed in medicine.

The ester of tropine with veratric acid

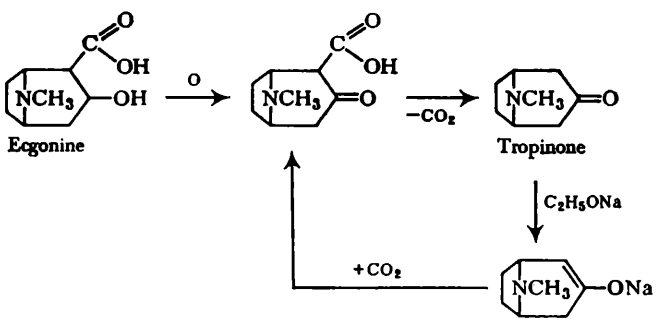


discovered in 1932 by A. P. Orekhov and R. A. Konovalova, is the alkaloid **convolamine**, which is present in certain species of bindweeds. Convolamine in which the >NH group rather than $>NCH_3$ is the bridge is called **convolvin** (an alkaloid discovered by the same authors).

Cocaine, $C_{17}H_{21}NO_4$, was first isolated by Niemann in 1860 from Peruvian coca leaves (*Erythroxylon coca*)

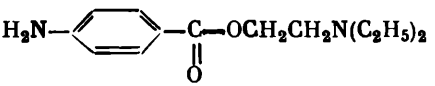


is the ester of a hydroxy acid of the tropane series, known as **ecgonine**. Cocaine can be converted by hydrolysis into ecgonine, benzoic acid and methanol. The successive esterification of ecgonine with benzoyl chloride (across the hydroxyl group) and methanol gives cocaine. This reaction establishes their relationships. Ecgonine in its turn is oxidized to a ketonic acid which is readily decarboxylated in aqueous solution, like β-ketonic acids, and is converted into tropinone. And, conversely, the sodium enolate of tropinone is carboxylated by the action of carbon dioxide into a ketonic acid:

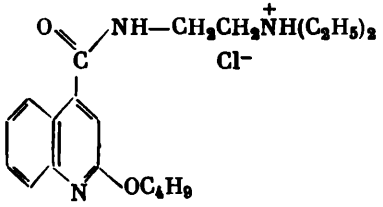


In this way the structures of ecgonine and cocaine are established. Hence, the Robinson synthesis of tropinone ends with the synthesis of cocaine (Willstätter).

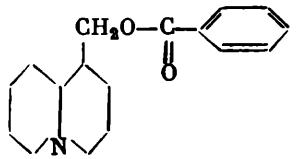
Cocaine was the first anesthetic to be discovered and therefore assumed great importance. Cocaine has serious disadvantages. It is toxic and habit-forming; it produces a condition of euphoria which may give rise to addiction (cocainism). This accounts for numerous searches for cocaine substitutes devoid of its shortcomings as an anesthetic, which were originally modelled upon the cocaine structure. Some of the most successful of these synthetic and semisynthetic anesthetics are novocaine (procaine), percaine, lupicaine.



Novocaine



Percaine

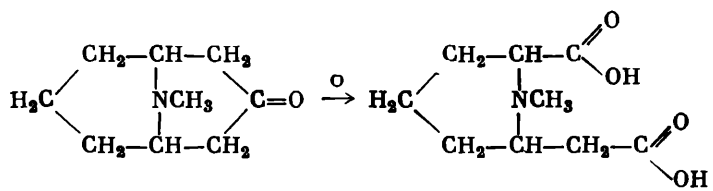


Lupicaine
(M. M. Katznelson, M. I. Kabachnik, 1935)

22.7. Alkaloids with Two Condensed Six-Membered Heterocycles Containing One Nitrogen Atom

Pseudopelletierine (*methylgranatanine*) is an alkaloid discovered in 1878 in the bark of the pomegranate tree (*Punica Granatum*). It was investigated by Ciamician and synthesized by Robinson. The structure of pseudopelletierine is analogous to that of tropinone, except that the basic structural unit of the compound in question is not tropane but a heterocycle consisting of two piperidine rings with the common system —CH—N—CH—.

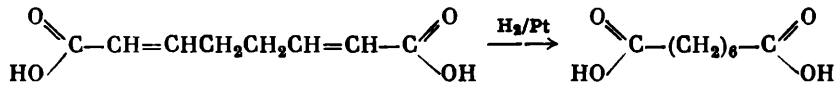
Pseudopelletierine is oxidized to **granatic acid** with the same number of carbon atoms (the analogue of tropinonic acid):



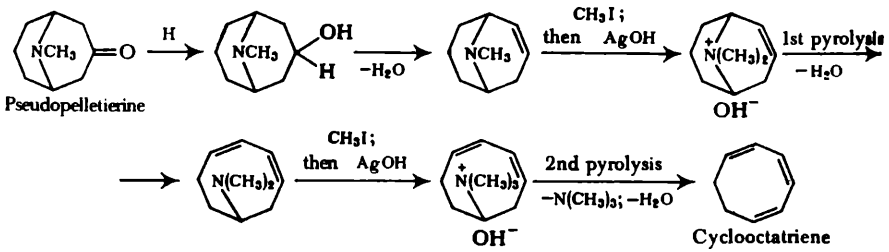
Pseudopelletierine Granatic acid

The Hofmann degradation of granatic acid leads to octadienic acid which on hydrogenation forms suberic acid (hexanedicarbox-

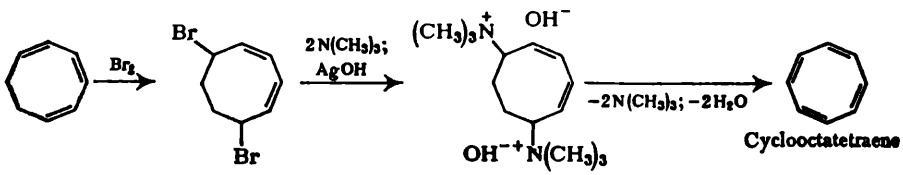
ylic acid):



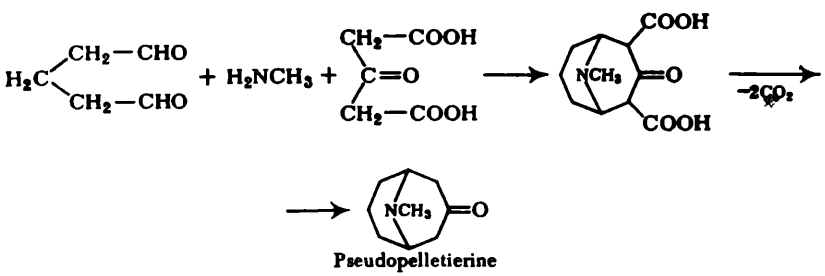
The Hofmann degradation of the alcohol, the reduction product of pseudopelletierine, which also proceeds in two steps but is accompanied by dehydration, leads to cyclooctatriene:



This route was used by Willstätter for the first synthesis of cyclooctatetraene (see Volume II, page 263). Bromine was added to the resulting cyclooctatriene and trimethylamine to the bromide, then bromine was replaced by a hydroxyl group and trimethylamine and water were eliminated from the hydroxide of a quaternary ammonium base by the Hofmann elimination reaction:



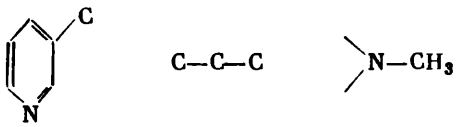
The synthesis of pseudopelletierine is analogous to that of tropinone (page 374), but the starting point is glutardialdehyde and not succindialdehyde:



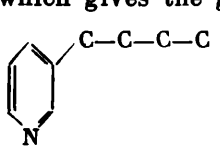
22.8. Alkaloids with Two Isolated Heterocycles Containing Two Nitrogen Atoms

The principal alkaloid of the tobacco plant, which contains 12 alkaloids, is **nicotine**, $C_{10}H_{14}N_2$. This is a liquid (b.p. 246°C at 730 mm Hg) with an unpleasant, stupefying odour, which is miscible with water at room temperature. Nicotine is very poisonous and has a powerful effect on the brain and the nervous system and increases the blood pressure. It is used in agricultural practice as an insecticide, for which purpose it is produced in large quantities as a by-product of the tobacco industry.

Nicotine contains two tertiary nitrogen atoms and is a strong base. When oxidized (HNO_3, $KMnO_4$) it gives **nicotinic acid** (β-pyridinecarboxylic acid). Treatment of nicotine with bromine followed by the oxidation of the bromination product yields the following compounds: the same β-pyridinecarboxylic acid, malonic acid, and methylamine, which proves the presence in nicotine of the following structural groups:



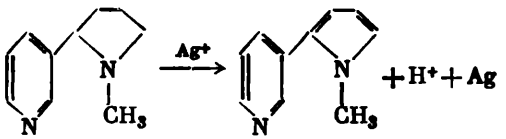
Since nicotine is a ditertiary base, the group $\rangle N—CH_3$ must close the ring. The group consisting of three carbon atoms (of malonic acid) must have been attached to the carbon of the carboxyl group of nicotinic acid, which gives the grouping



This makes probable the structure of nicotine as (N-methyl-α-pyrrolidyl)-β-pyridine since of the four carbon atoms of the chain it is possible to cyclize, by means of the group $\rangle N—CH_3$, either the five-membered pyrrolidine ring or the lower rings, which are almost improbable on account of their instability.

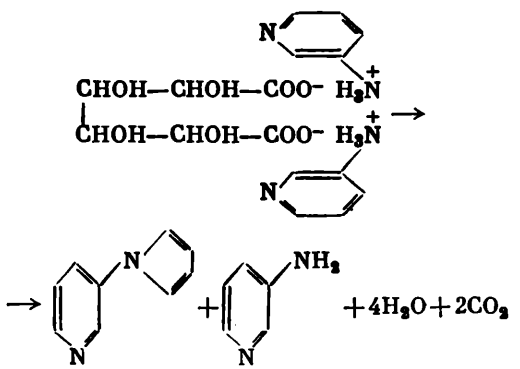
When oxidized with silver acetate the pyrrolidine ring of nicotine converts into the pyrrole ring and **nicotyrine** is formed, which is

also present in the tobacco plant:

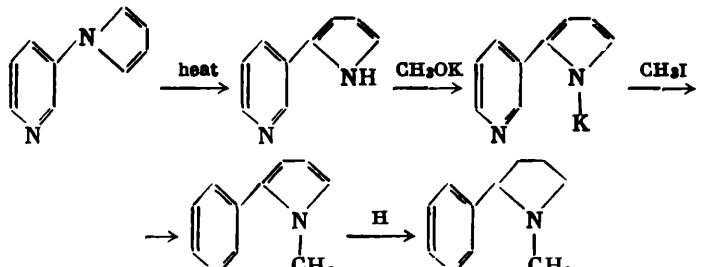


Nicotine Nicotyrine

Pictet effected the synthesis of nicotine as follows. First N-pyrryl-β-pyridine was obtained by the pyrolysis of the salt of mucic acid and β-aminopyridine (this synthesis is analogous to the synthesis of pyrrole by the pyrolysis of ammonium mucate):



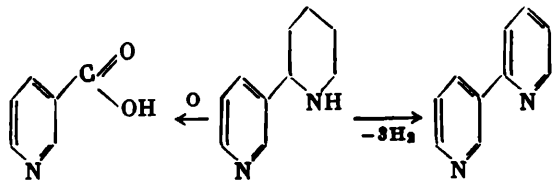
When heated the N-pyrrole derivative was isomerized to the C-pyrrole α-derivative (see Volume III, page 341). The synthesis then takes the following route:



Nicotyrine Nicotine

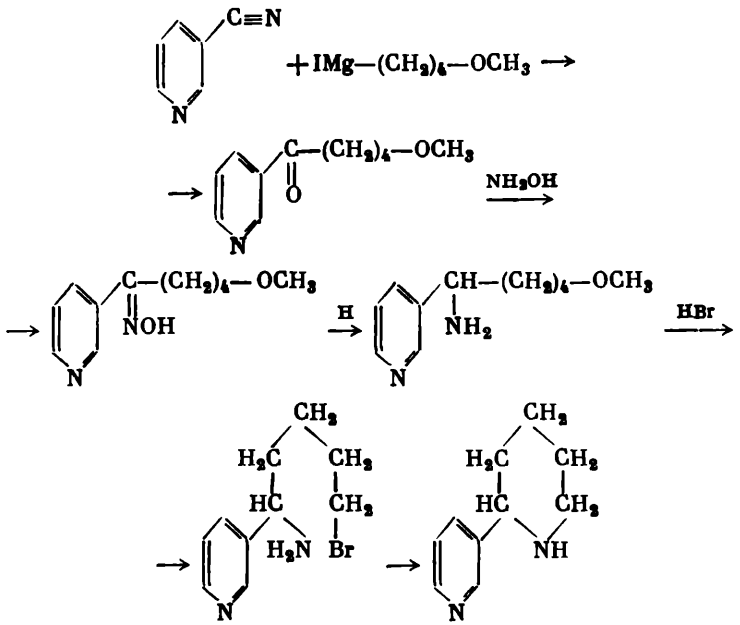
An isomer of nicotine is **anabasine** (*neonicotine*) discovered in 1929 by A. P. Orekhov in the leafless echinochloa plant growing in the Soviet Central Asia. Anabasine is miscible with water. It is a strong diatomic base; one of the nitrogen atoms is in the form of a secondary amino group. When oxidized anabasine is converted into nicoti-

nic acid, and when subjected to dehydrogenation it gives α,β-dipyridyl. All these facts enabled Orekhov to establish the structure of α-piperidyl-β-pyridine for anabasine:



Anabasine

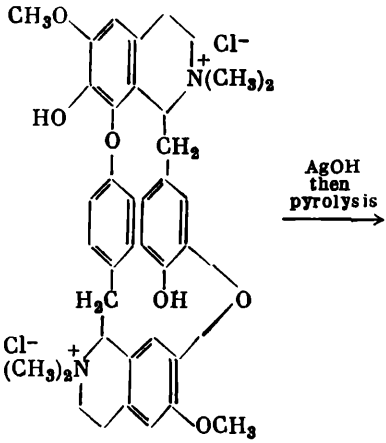
The synthesis of anabasine was accomplished by G. P. Menshikov by the following scheme:



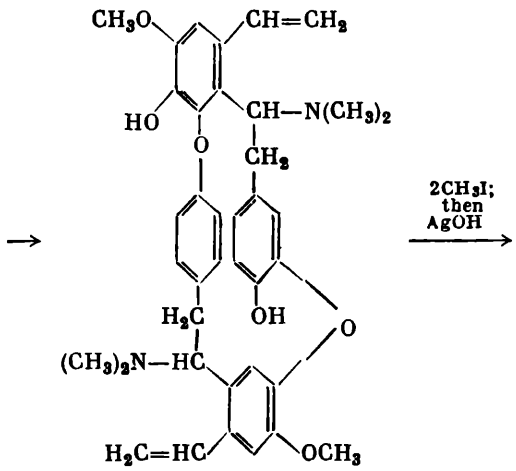
Anabasine, like nicotine, is used as an insecticide.

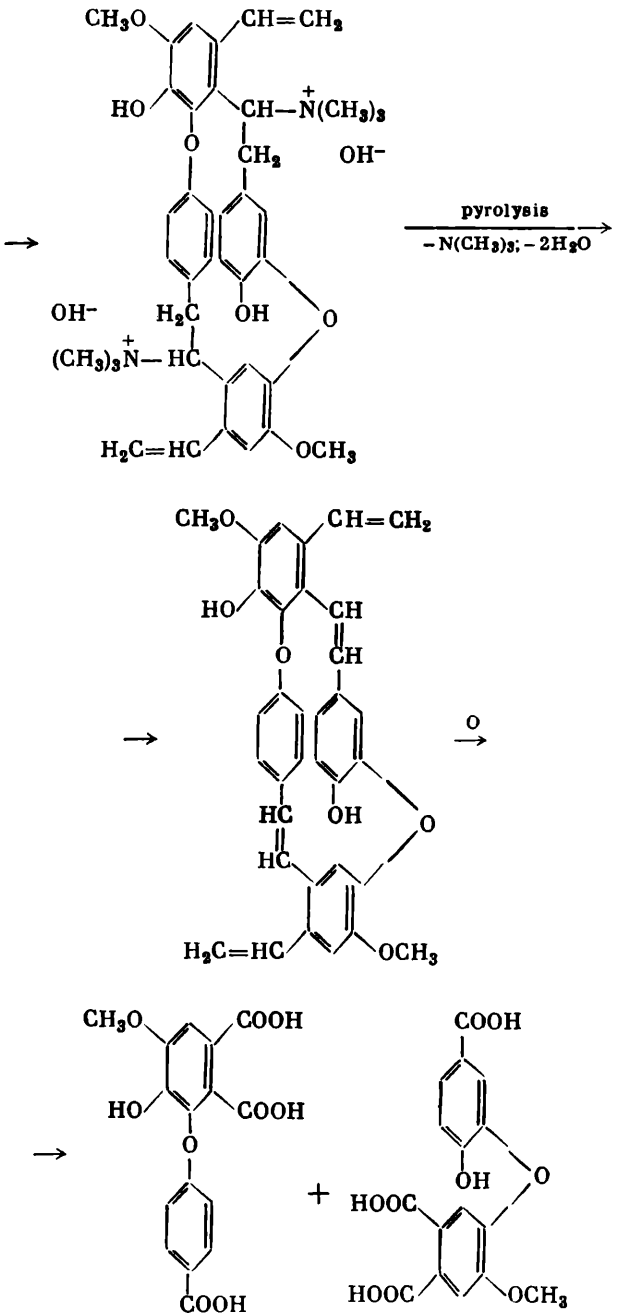
D-**Tubocurarine** is one of the alkaloids present in the bark of South American plants of the *Strychnos* species, which was used by the Indians as a paralyzing arrow and dart poison. The related alkaloids of similar structure and physiological effect are L-curine, protocuridine, etc. Tubocurarine is the most powerful of the curare alkaloids. It has the ability to prevent the transmission of the nerve impulse at the neuromuscular junction, inducing a muscular relaxation and, in sufficient dosage, causing death by paralysis of the respiratory muscles (a muscular paralyzant). It is a valuable clinical drug,

inducing a muscular relaxation that permits surgery to be performed more effectively and at a lower degree of general anesthesia. D-Tubocurarine (its structure was established by King, Wintersteiner and Dutger) is a diquaternary ammonium salt (chloride) and has the molecular formula $C_{38}H_{44}O_6N_2Cl_2$. Both chlorine atoms are ionic; of the oxygen atoms two are phenolic, two are methoxyl oxygen atoms attached to the aromatic rings, and the remaining two are ethereal. The Hofmann degradation may be applied to tubocurarine only after the chlorine atoms have been replaced by hydroxyl ions. The formula of tubocurarine can be built up on the basis of the degradation products. The Hofmann degradation (twice) followed by the oxidation of the base proceeds as shown on the scheme:



D-Tubocurarine



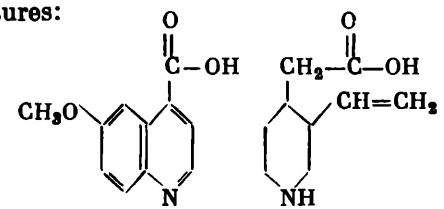

CH3O
CH=CH2
HO
CH—N(CH3)3
O
CH2
OH-
pyrolysis
-N(CH3)3; -2H2O
OH-
H2C
OH
O
(CH3)3N—HC
H2C=HC
OCH3
CH3O
CH=CH2
HO
CH
O
CH
HC
OH
O
HC
H2C=HC
OCH3
O
CH3O
COOH
HO
COOH
O
COOH
+
COOH
OH
O
HOOC
HOOC
OCH3

22.9. Alkaloids with Two Condensed Six-Membered Heterocycles Containing One Common Nitrogen Atom and One Isolated Heterocycle

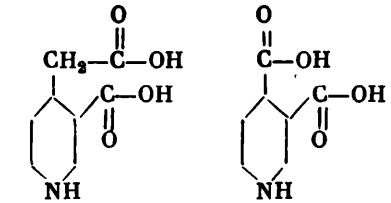
In 1820 Pelletier and Caventou isolated two alkaloids from the cinchona bark—**quinine** and **cinchonine.** Quinine is one of the most valuable medicines used for the control of the symptoms of malaria: it acts by destroying the malarial parasite. It also serves as the starting point in the synthesis of antimalarial drugs.

Quinine is a methoxy derivative of cinchonine. By reaction of quinine with potassium hydroxide under vigorous conditions A. M. Butlerov and A. N. Vyshnegradsky for the first time obtained quinoline (from which the name quinine was derived).

Quinine is a diatomic base. With methyl iodide it gives diiodomethoxide (at both nitrogen atoms); with hydrogen iodide it loses CH_3I (due to the presence of a methoxy group); with benzoyl chloride quinine forms monobenzoic ester (due to the presence of a hydroxyl group). Quinine can be oxidized to give the ketone quininone (because of the presence of a secondary alcoholic group). The molecule of quinine contains one active double bond and the oxidation with permanganate is directed to this bond; this gives rise to a carboxylic acid containing one carbon atom less than quinine. Hence, this double bond belongs to the $CH_2{=}CH$ group of the side chain. Upon more energetic oxidation both this acid and quinine itself form identical products (the products, except those resulting from meroquinene, will be discussed at a later time). These products include, in the first place, **quininic acid,** $C_{11}H_9O_3N$, isolated by A. A. Voskresensky, which has been found to be 6-methoxyquinoline-4-carboxylic acid (6-methoxycinchoninic acid). Cinchonine on analogous oxidation gives quinoline-4-carboxylic acid or **cinchoninic acid.** Moreover, the "second half" (as described by Skraup) of the quinine and cinchonine molecules on oxidation gives identical fragments of differing degrees of degradation: meroquinene, cincholoiponic acid, and loiponic acid, which were identified as the derivatives of piperidine. Thus, the oxidation products of quinine have the following structures:



Quininic acid Meroquinene

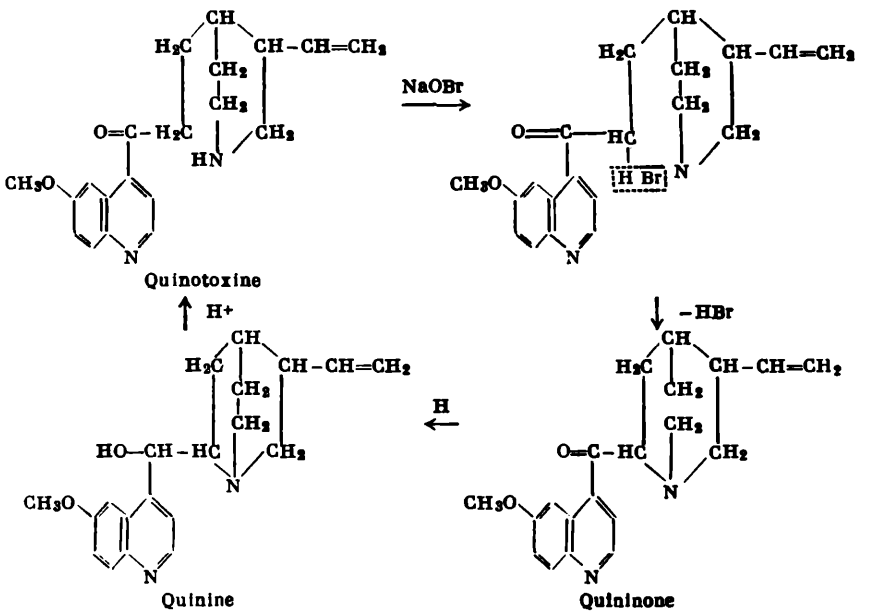


Cincholoiponic acid — Loiponic acid

In all the piperidine products of oxidation of quinine and cinchonine, the nitrogen is secondary, whereas quinine has no secondary nitrogen.

As early as Pasteur discovered that quinine when heated with acids isomerizes to the ketone **quinotoxine** (this is one more alkaloid of the cinchona bark). Quinotoxine contains a secondary amino nitrogen (evidenced by acylation, and nitrosation across >NH); it can be converted back to quinine (Rabe) by way of bromination (NaOBr) across the secondary amino group to give bromoamine BrN< and subsequent ring closure upon elimination of HBr with alkali. The hydrogen can be eliminated in this case only from the α-position with respect to the keto group. This gives the ketone **quininone**, the oxidation product of quinine, which is reduced to the secondary alcohol quinine.

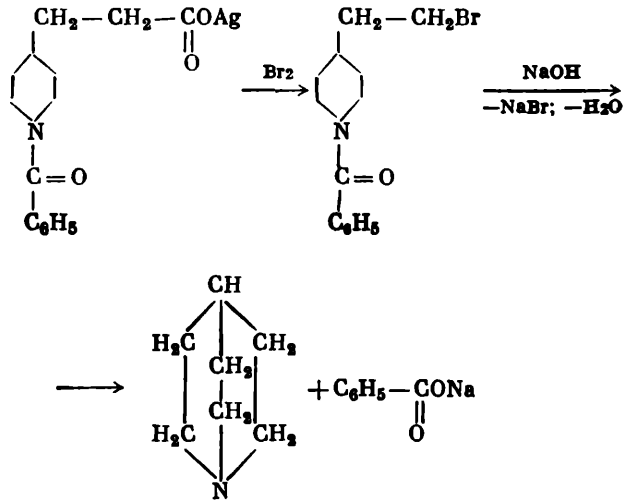
All these facts are in keeping with the following formulas of quinine and quinotoxine:



Analogous transformations are known for cinchonine too.

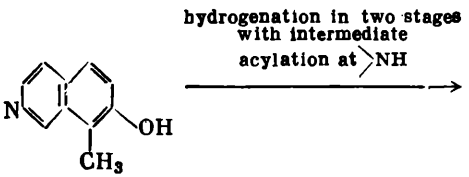
Thus, both these alkaloids are each a combination of two heterocyclic nuclei—the quinoline nucleus and the quinuclidine nucleus, which are joined together via a carbon atom with a secondary alcoholic group.

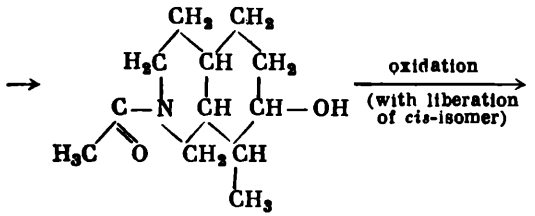
Quinuclidine is a heterocyclic system consisting of two piperidine rings fused together via the nitrogen atom and the γ-carbon. It was synthesized (Rubtsov) in the following way:

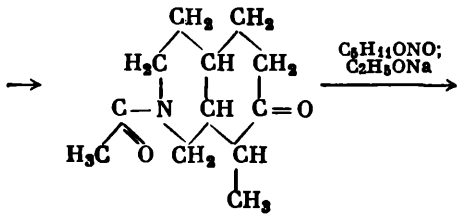


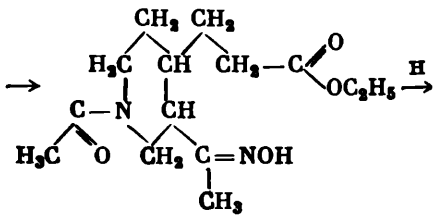
Quinuclidine

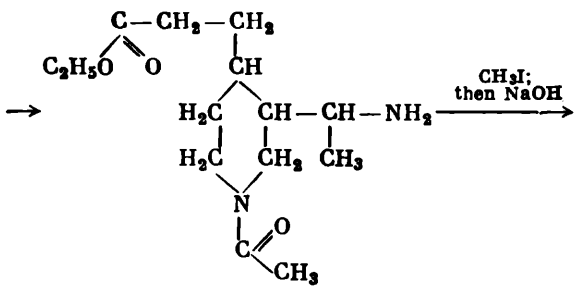
Rabe carried out the synthesis of dihydroquinine. The synthesis of quinine itself (with a vinyl group) was accomplished in 1944 by R. B. Woodward and W. E. Doering. It involved the following stages: (1) the synthesis of racemic homomeroquinene with the side chain containing one more CH_2 group as compared with meroquinene; (2) the ester condensation of quininic acid with the ester of homomeroquinene at the α-methylene unit of the latter; (3) the saponification and decarboxylation (ketonic cleavage) of the resulting ester of the β-keto acid and the subsequent preparation of racemic quinotoxine which is resolved into L- and D-quinotoxines; (4) the conversion of the D-isomer into quinine by Rabe's method. Below is shown the synthesis of homomeroquinene:

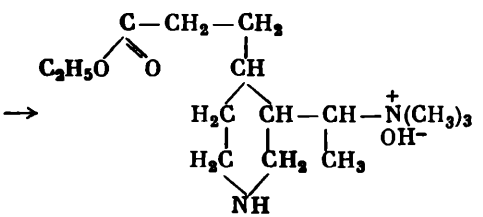


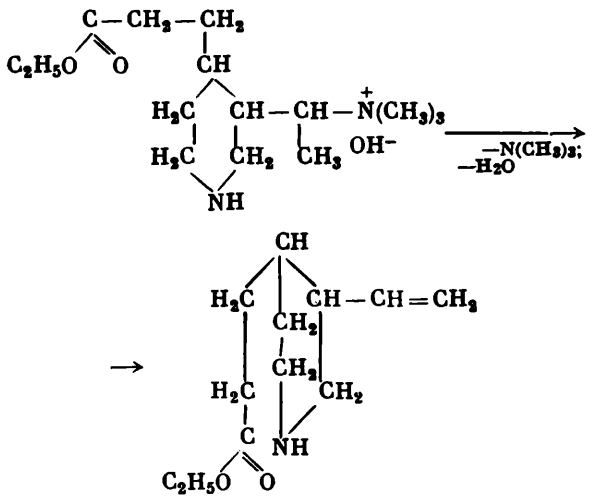

oxidation
(with liberation of cis-isomer)


$C_8H_{11}ONO$;
C_2H_5ONa


H

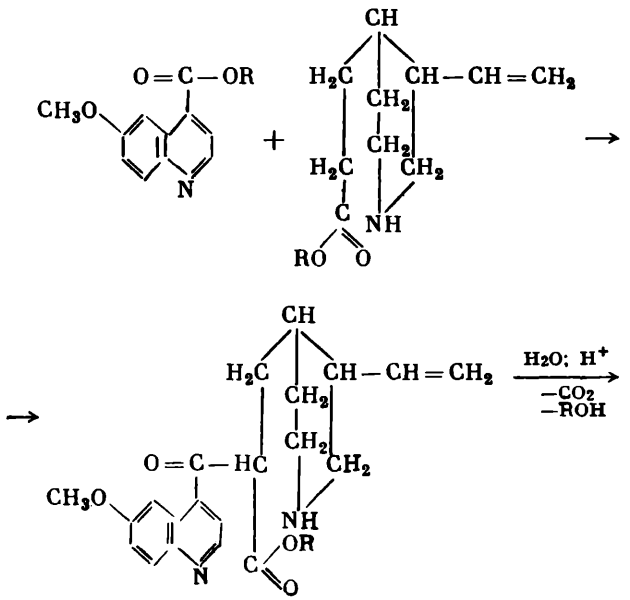

CH_3I;
then NaOH

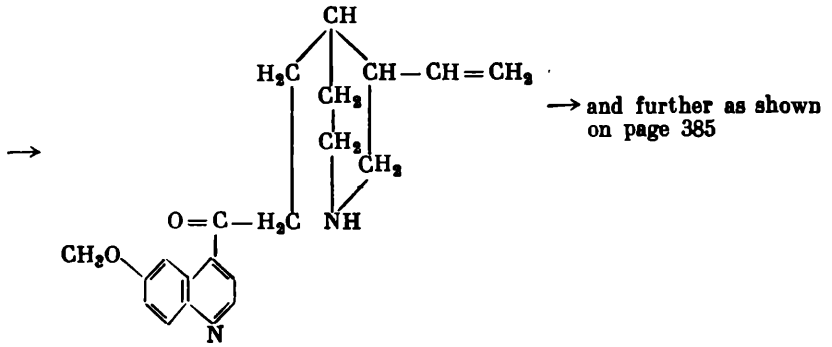




Ester of homomeroquinene

The longest series of conversions had to be carried out in order to synthesize homomeroquinene (only the briefest outline of the synthesis is given). The ester condensation of the ester of quininic acid with the ester of homomeroquinene (stage 2) and decarboxylation (stage 3) were effected by the following scheme:





Quinotoxine

22.10. Alkaloids with Three Condensed Heterocycles Containing Two Nitrogen Atoms

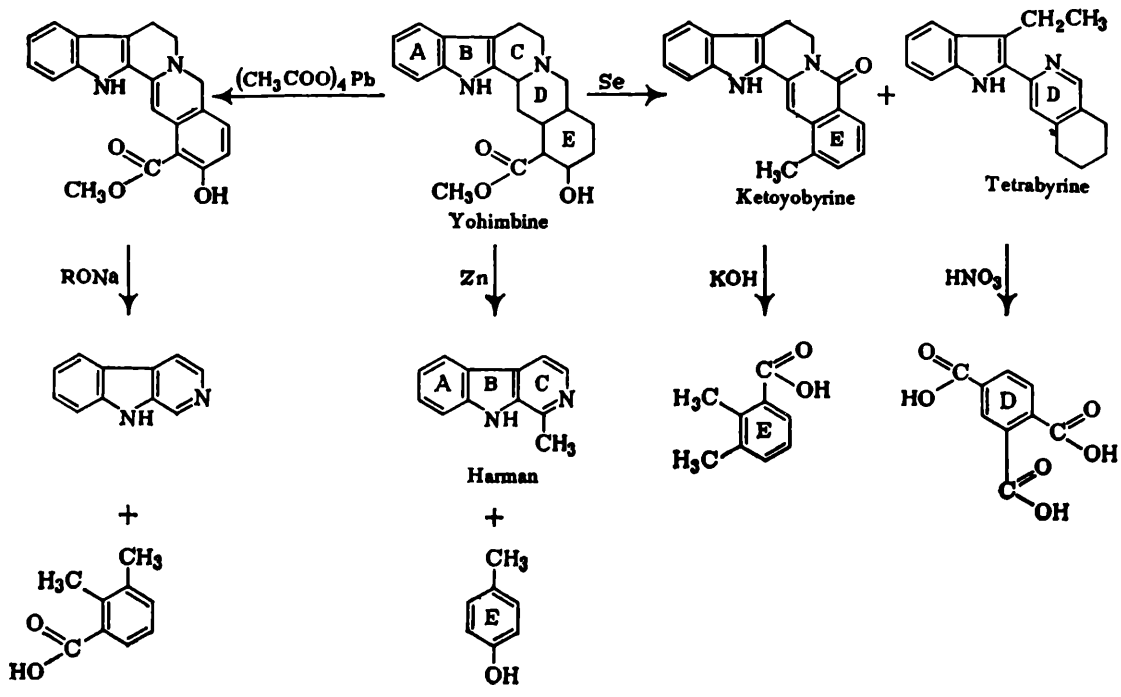
We shall limit ourselves to the structures of only two alkaloids of this group—yohimbine and reserpine.

Yohimbine is an alkaloid from the bark of the African plant Yohimbé (*Coryanthe johimbe*), where it is present along with a number of its isomers.

The structure of the yohimbine skeleton follows from the products formed as a result of the conversions shown on page 390.

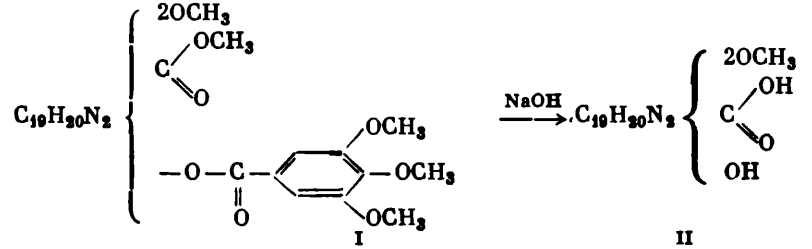
The dehydrogenation of yohimbine with selenium yields a several compounds, one of which, **tetrabyrine**, on oxidation gives pyridine-2,4,5-tricarboxylic acid, and another one, **ketoyobyrine**, gives 2,3-dimethylbenzoic acid. The former acid can be formed only due to the D ring left (ring C has only two links to carbons and is able to form, at most, a pyridinecarboxylic acid). 2,3-Dimethylbenzoic acid cannot probably be formed due to the rings A, B, C, D and is a residue of ring E. The disposition of carboxyl groups in pyridine-2,4,5-tricarboxylic acid and also of the methyl and the carboxyl group in 2,3-dimethylbenzoic acid indicates the points of junction between rings D and E and the position of the carboxyl group in ring E. The position of the hydroxyl group in ring E is deduced from the decomposition of yohimbine by distillation with zinc dust, which results in the formation of small amounts of harman and *p*-cresol.

Reserpine, $C_{33}H_{40}N_2O_9$, is an alkaloid present in the roots of species of the Indian plant *Rauwolfia serpentina*. It has been used since 1950 as one of the most important medicines in the treatment of high blood pressure (hypertension) and also as a tranquilizer for the emotionally disturbed. On alkaline hydrolysis reserpine yields


(CH3COO)4 Pb
Se
Yohimbine
Ketoyobyrine
Tetrabyrine
RONa
Zn
KOH
HNO3
Harman

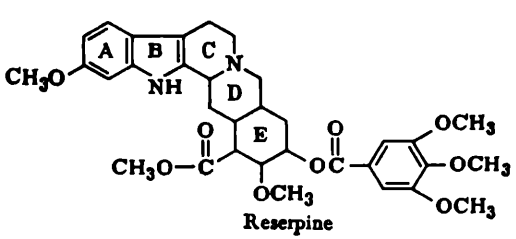
methanol and 3,4,5-trimethoxybenzoic acid, forming reserpic acid, $C_{22}H_{27}O_5N_2$. This acid when methylated at the carboxyl group with diazomethane is esterified by 3,4,5-trimethoxybenzoyl chloride to reserpine, which proves the retention of the skeletal structure of reserpine in these conversions and the role of methanol and trimethoxybenzoic acid.

Functional analysis of reserpine reveals the presence of five methoxyl groups and one carboxyl group. Thus, the partial structure of reserpine may be expressed by formula I, and that of reserpic acid, by formula II:

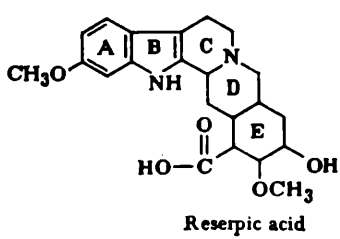


The ultraviolet absorption spectra of reserpine, reserpic acid, reserpic alcohol, and a mixture of the last two compounds have a shape characteristic of the derivatives of indole, and are close to the spectrum of 2,3-dimethyl-6-methoxyindole (Fig. 22.1). The infrared spectra of chloroform solutions of reserpine (Fig. 22.2) and an equimolar mixture of molecules containing some fragments of its structure are nearly the same. Such an equimolecular mixture consists of 2,3-dimethyl-6-methoxyindole (a fragment corresponding to rings A and B), N-ethylpiperidine (rings C and D), methyl ester of cyclohexanecarboxylic acid (ring E), and the methyl ester of 3,4,5-trimethoxybenzoic acid. The solid line is the spectrum of reserpine, the line with dotted portions represents the spectrum of the mixture indicated (Fig. 22.3). A comparison with the spectrum of the synthesized model pentacyclic system ABCDE of similar structure has confirmed the analogy between this structure and the structure of reserpic acid (and of yohimbine).

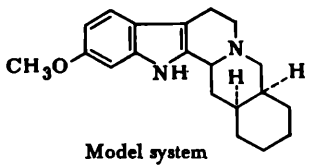
This comparison has also elucidated the *cis*-junction between rings D and E in reserpic acid and reserpine:



Reserpine



Reserpic acid



Model system

The fusion of reserpic acid with alkali leads (after the methylation of the fused mass fraction containing the acid) to the methyl ester

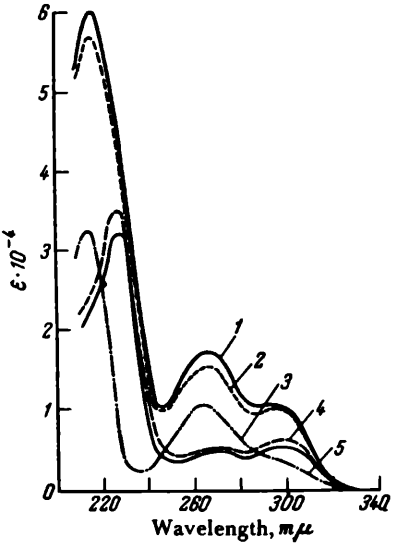


Fig. 22.1

Ultraviolet (UV) spectra (in methanol):

1—reserpine; *2*—equimolar mixture of reserpine alcohol and methyl ester of 3,4,5-trimethoxybenzoic acid; *3*—methyl ester of 3,4,5-trimethoxybenzoic acid; *4*—reserpine alcohol; *5*—2,3-dimethyl-6-methoxyindole.

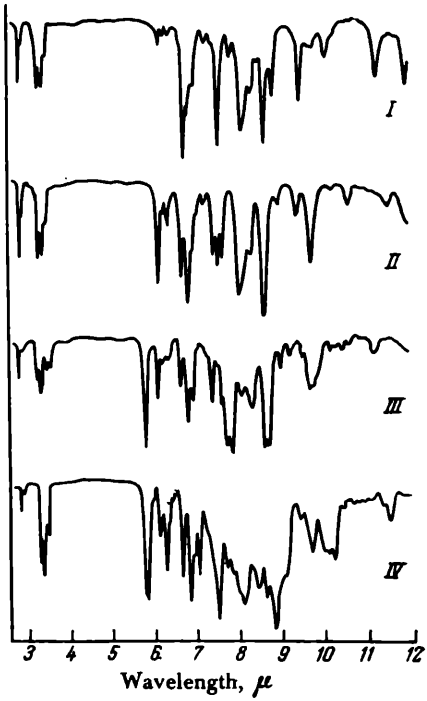


Fig. 22.2.

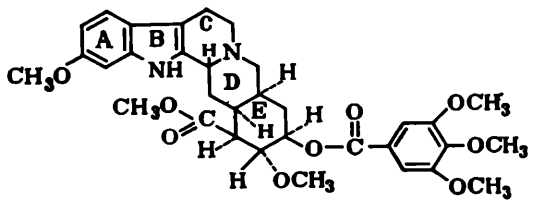
Infrared (IR) spectra (in chloroform):

I—2,3-dimethyl-5,6-dimethoxyindole; *II*—2,3-dimethyl-6-methoxyindole; *III*—tetrahydroalstoniline; *IV*—reserpine.

of 3-methoxyisophthalic acid, which proves the position of the hydroxyl group in reserpine (the α-methoxyl group of ring E is eliminated as CH_3OH and forms one of the double bonds).

The synthesis of reserpine accomplished by Woodward and his coworkers in 1957 proved to be a very formidable task, considering

the involved stereochemistry of the molecule, which is reflected in the following formula:



Reserpine

The synthesis begins with the construction of the structure and configuration of rings D and E, for which purpose benzoquinone is condensed by the Diels-Alder reaction (*cis*-addition) with vinylacrylic acid. The resulting bicyclic compound I is reduced with sodium

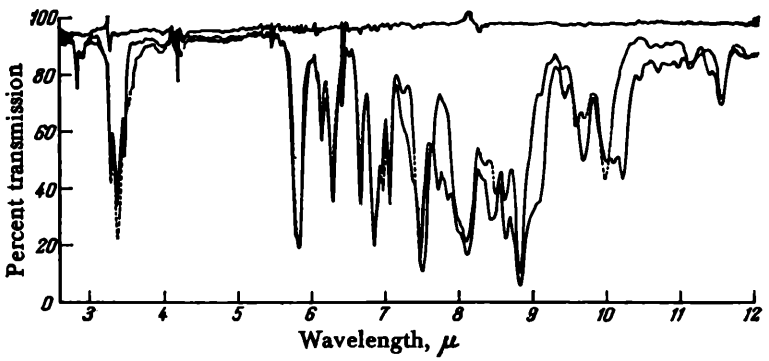
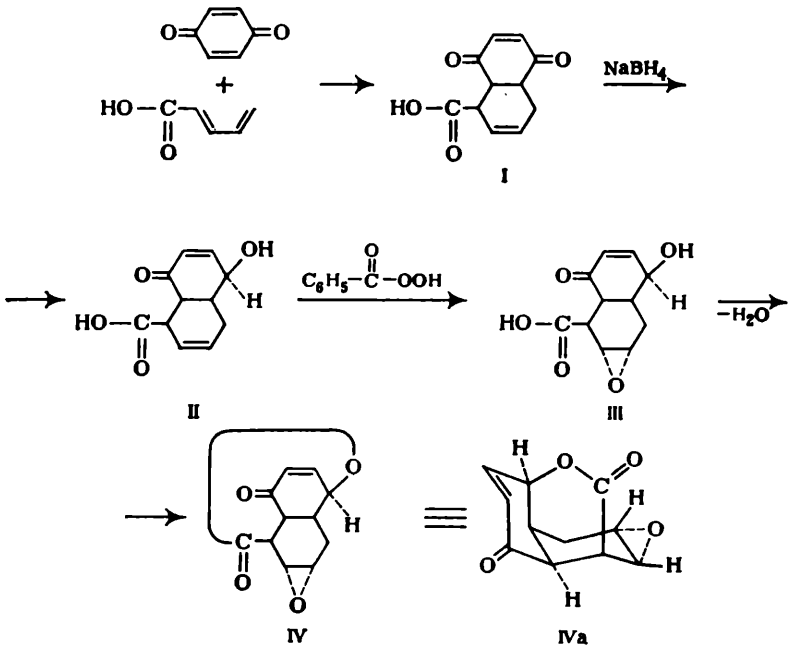


Fig. 22.3.

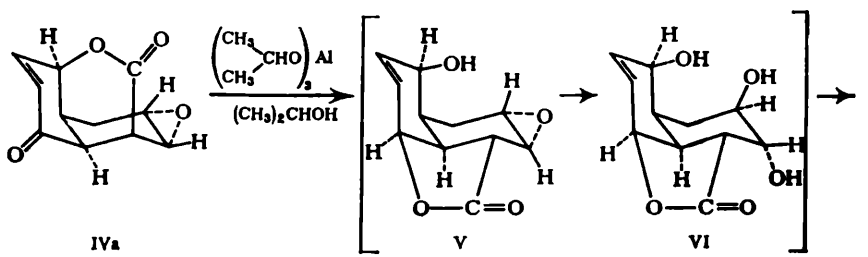
The infrared spectra of reserpine (heavy line) and equimolar solution of 2,3-dimethyl-6-methoxyindole, methyl 3,4,5-trimethoxybenzoate, methyl cyclohexanecarboxylate: and N-ethylpiperidine in chloroform (heavy line with broken portions). The upper curve shows calibration peaks of CO_2 (4.224 μ) and H_2O (5.464 and 6.41 μ).

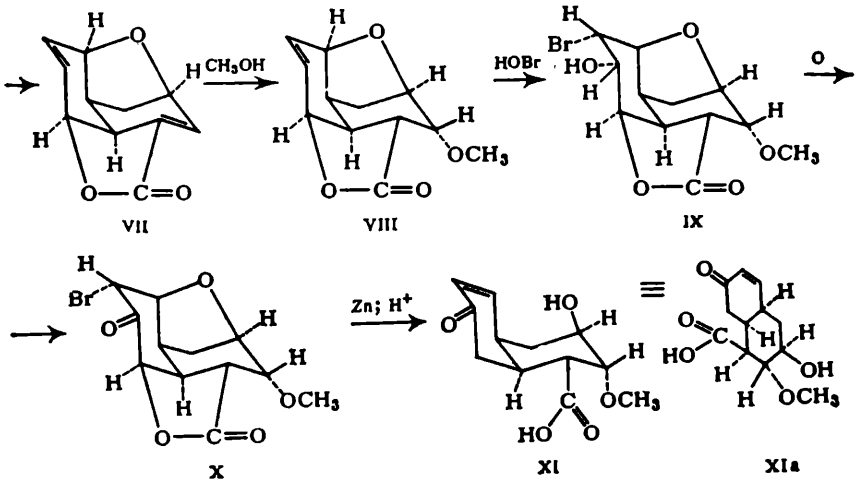
borohydride across the less sterically hindered keto group to compound II which is oxidized further with perbenzoic acid to epoxide III (the oxygen bridge is added from the external, more opened side of the spatial angle formed by the rings). When the epoxide III is reacted with dehydrating agents, lactone IV is formed at the expense of the carboxyl and hydroxyl groups introduced upon conversion of I into II. Lactone IV may be presented by the perspective formula IVa

which is identical with IV:

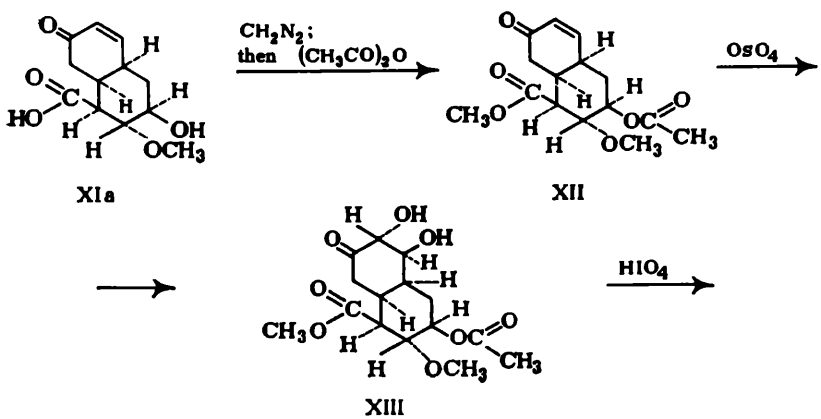


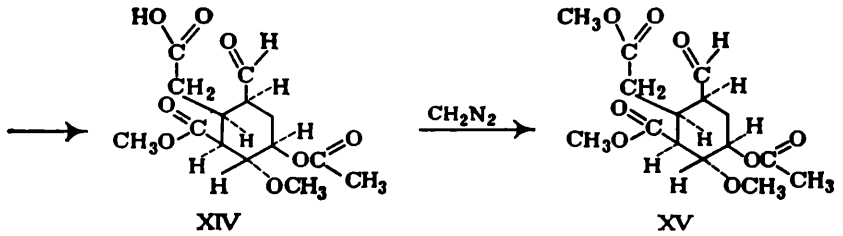
The reduction of the lactone with isopropyl alcohol in the presence of aluminium isopropoxide results in the conversion of the carbonyl group left into a secondary alcoholic group, this being accompanied by the opening of the lactone ring and by the cyclization of the carboxyl group to a new hydroxyl group. Besides, the epoxide ring is opened with the formation of a glycol; one of its hydroxyls undergoes cyclization with the liberated hydroxyl to form an ether bridge, and the other is eliminated as water with the formation of a double bond in the ring. All these reactions, which take place at a single stage, are presented separately in formulas IVa-VII.





To compound VII is added methanol (VIII) across the C=C bond conjugated with the carboxyl group, which is followed by addition of hypobromous acid to the second double bond (IX). The secondary alcoholic group of bromohydrin is oxidized to the keto group and the resulting compound X is treated with zinc in acid medium. Both heterocycles, the lactone ring and the ether ring, are opened at the C—O bonds (the latter does so with the simultaneous elimination of bromine and formation of a double bond at the site of the eliminated Br and O). This gives rise to compound XI, the formula of which may be written more simply in the plane of XIa. Further conversions are clear from formulas XIa-XV:





XIV XV

The compound XV serves then as the starting point for the synthesis of the rings E and D of reserpine.

It now remains to build up the remaining portion of the reserpine skeleton, rings A and B (see the scheme on page 398).

This is accomplished by starting from the magnesium derivative of 6-methoxyindole (XVI), which is reacted with the nitrile of monochloroacetic acid. As is always the case in indole, the substituent enters the β-position and the nitrile of 6-methoxy-β-indolylacetic acid (XVII) is formed. It is then reduced to an amine—6-methoxytryptamine XVIII, which reacts with aldehyde XV and is converted into a Schiff's base XIX. This Schiff's base is reduced to an amine XX, which undergoes cyclization with loss of CH_3OH to give a cyclic amide XXI (the formation of ring D). Cyclization to give the C ring is effected by phosphorus oxychloride which reacts with XXI: now the compound XXII has all the rings required, A, B, C, D, and E.

By reacting XXII with sodium borohydride, the ammonium nitrogen is reduced to the amine nitrogen, and then both ester groupings are hydrolysed to give XXIII. The liberated carboxyl and hydroxyl groups of compound XXIV undergo cyclization under the action of dicyclohexylcarbodiimide to form the lactone XXV. The last compound on heating with dilute acid stereoisomerizes with respect to the arrangement about the carbon atom common to rings C and D (stereoisomer XXVI). Then the lactone ring is opened by the action of acidified methanol, and the liberated hydroxyl group of compound XXVII is esterified with the acid chloride of trimethylgallic acid.

Reserpine XXVIII, which is identical with the natural compound, is synthesized in this way. The total synthesis is shown on the scheme given on page 398.

Strychnine, $C_{21}H_{22}O_2N_2$, and **brucine**, $C_{23}H_{26}O_4N_2$, were isolated in 1818 by Pelletier and Caventou from the seeds of *Strychnos nux vomica*, which grows in Indonesia. Both these alkaloids, notably strychnine, are highly poisonous compounds (the lethal dose for man is 0.03 g), which produce convulsions. These are crystalline compounds soluble in alcohol, benzene, chloroform, slightly soluble in water and ether, and are optically active. Strychnine is used in medicine as a stimulant and a tonic.

Brucine is a dimethoxy derivative of strychnine and is used, along with strychnine, in the stereochemical experiment for resolution of racemates of acids. The final formula of strychnine was established in 1945 by Robinson after investigations that spanned over more than a century; this also led to elucidation of the structure of brucine (page 399). We can give here only the briefest outline of the facts and reasoning underlying these formulas.

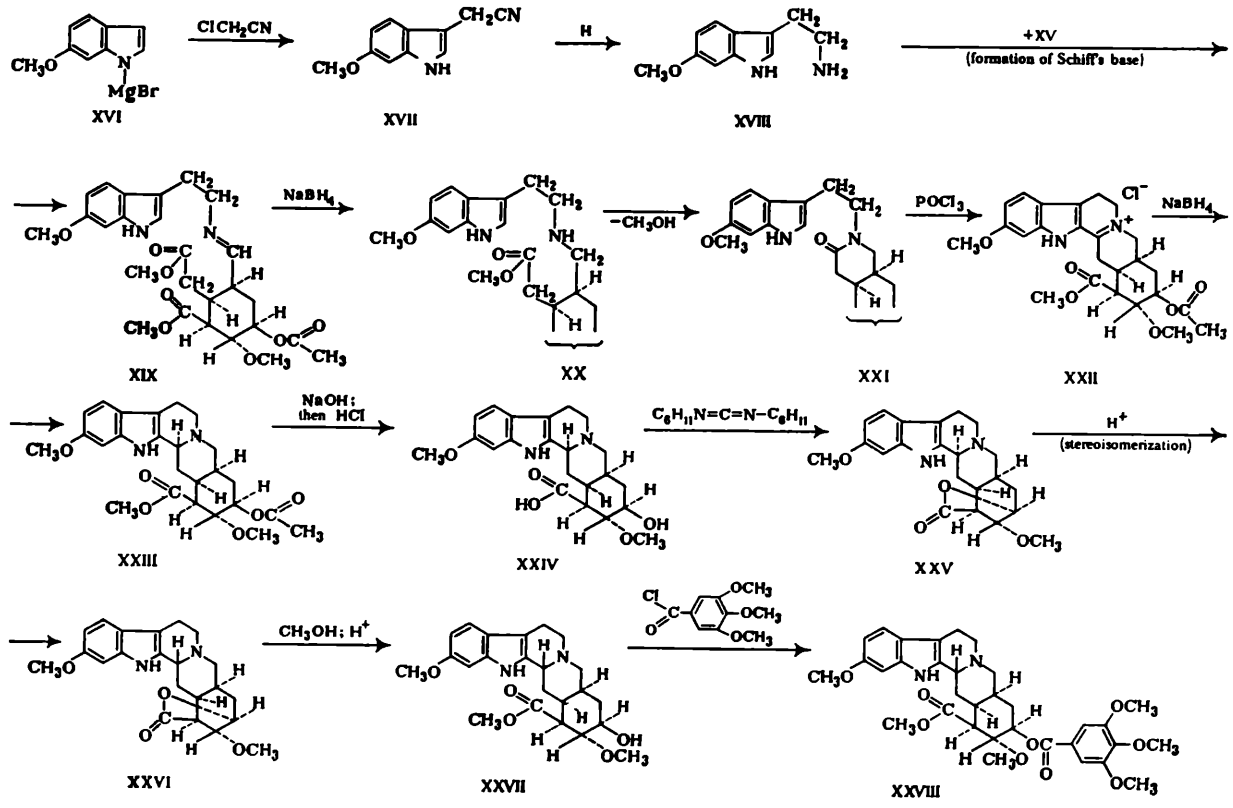
When strychnine is oxidized with nitric acid, 5,7-dinitro-indole-2,3-dicarboxylic acid results, from which it follows that strychnine (and, hence, brucine too) contains the indole ring. Both compounds contain each one olefinic double bond (since they are catalytically hydrogenated to dihydro alkaloids) and two nitrogen atoms. The nitrogen atoms are both tertiary, but only one of them is basic and is capable of adding methyl iodide; the other nitrogen atom is deprived of basic properties since it is acylated (linked to the CO group), which is evidenced by the results of alkaline hydrolysis. This leads, due probably to the opening of the cyclic lactam ring, to strychnic acid (or brucinic acid in the case of brucine) in the form of a salt. The acid is richer by one H_2O unit than the parent base and contains a secondary, already basic, amino group (acylation, the action of HNO_2).

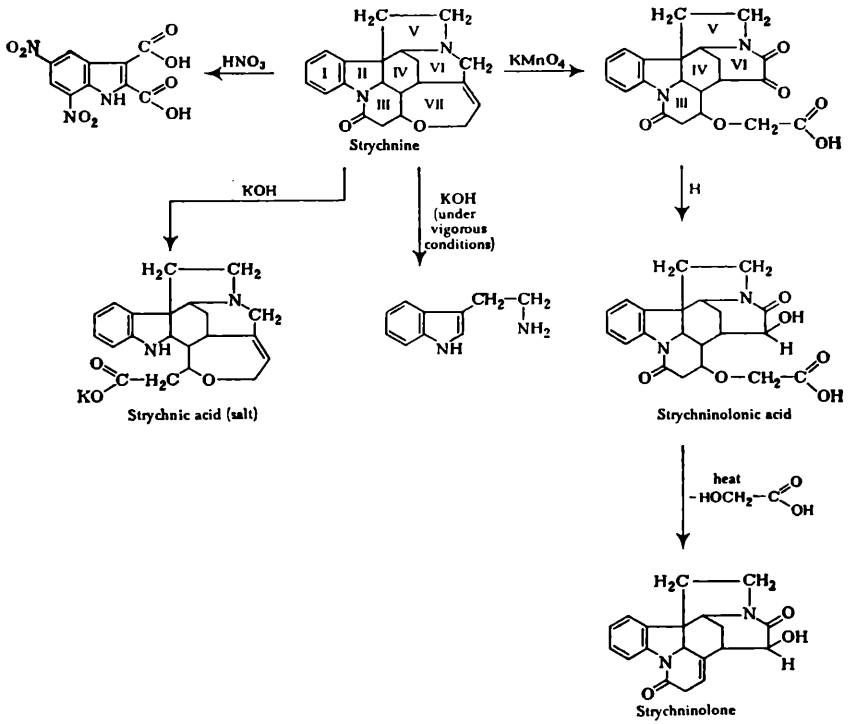
Since these acids have two basic nitrogen atoms, it is clear that the indole ring is in the heterocycle-hydrogenated state in them (2,3-dihydroindole).

Both these acids can easily be cyclized into alkaloids. Adjacent to the lactam CO group, which acylates the dihydroindole nitrogen, is a CH_2 group since both strychnine and brucine undergo nitrosation at carbon, forming isonitroso derivatives, and condense with benzaldehyde to give benzylidene derivatives. The second oxygen atom (the ether oxygen) enters the ring and, separated from it by two carbon atoms in the ring is the above-mentioned olefinic double bond, which is the first to be broken on oxidation with permanganate with formation of a carboxyl group from one side of the ruptured ring and a carbonyl group from the other. The reduction of the active CO group and heating results in the elimination of glycolic acid.

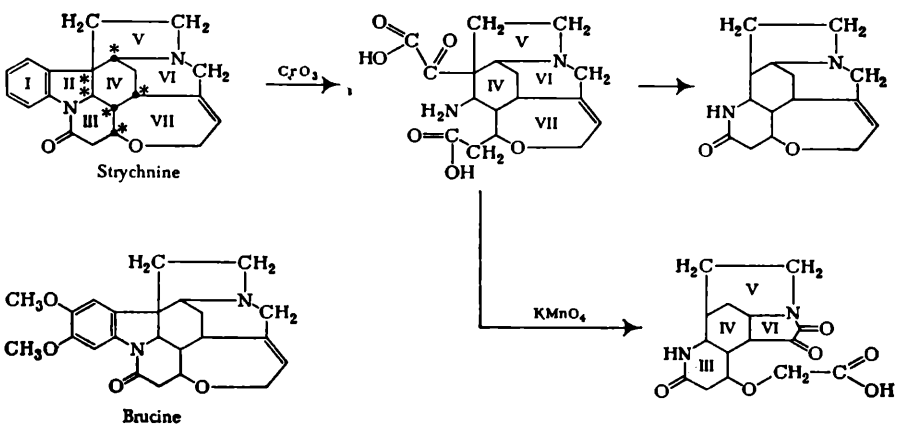
The oxidation of strychnine, the subsequent degradation of the molecule and the series of conversions mentioned above may be formulated by the scheme shown on page 399.

The course of the degradation processes furnishes some idea of the structure and interconnection of rings I, II, III, and VII. The conversion effected by the action of alkali into β-(β-aminoethyl)-indole, or **tryptamine**, throws light on the mode of bonding between the second nitrogen atom and the indole ring. The series of oxidation reactions brought about by chromic acid (the double bond is protected), shown by the scheme below, provides information on the rings IV, V, and VI.


ClCH2CN
H
+XV
(formation of Schiff's base)
XVI
XVII
XVIII
NaBH4
-CH3OH
POCl3
NaBH4
XIX
XX
XXI
XXII
NaOH;
then HCl
C6H11N=C=N-C6H11
H+
(stereoisomerization)
XXIII
XXIV
XXV
CH3OH; H+
XXVI
XXVII
XXVIII



It is obvious that the molecule can be simplified further by eliminating glycolic acid and opening both piperidine rings.



The structure of strychnine has very recently been confirmed by the highly involved synthesis carried out by Woodward. Especially difficult in the synthesis of such complex structures is the realization of the stereochemical requirements: strychnine contains six asymmetric atoms which are marked with asterisks in the above formula.

The heavy dots signify (according to Linstead) carbon atoms bearing hydrogens which are above the plane of the paper.

Chapter 23

Proteins

The cells of all living organisms—animals, plants, and the smallest cellular organisms—contain proteins as the vital component, which build up enzymes, organelles and the cell protoplasm as a whole. The particles of the simplest organism-like formations, viruses, are also composed of proteins and nucleic acids.

Proteins are the structural material of all known forms of life. All proteins (with the exception of those obtained synthetically in the last years) are produced by the vital activity of organisms, but not all of them continue to participate in life processes. Wool, skin, silk, cobweb, horns, nails, feathers, and hoofs are all proteins called scleroproteins. Proteins include albumins (egg albumin, blood albumin) and globulins (from blood), which are soluble in water or salt solutions, the myosin of muscle, numerous plant proteins, in particular, the proteins of plant seeds, such as gliadin (from wheat) and zein (from maize or wheat).

Special kinds of proteins are numerous enzymes of animal and plant organisms, such as the digestion enzymes—pepsin, chymotrypsin, trypsin, the various peptidases and other proteolytic enzymes, esterases, say, cholinesterase (page 461).

Some important hormones (insulin, adrenocorticotropic hormone, glucagon, etc.) are also proteins. As has been established, strictly individual proteins, which perform identical functions, may differ from one another in different organisms. Thus, human insulin, pig insulin and cow insulin differ in structural details, though they are similar in their function and interrelations.

From what has been said it follows that proteins are substances having quite different physical properties. Their primary classification was based on their physical properties and on their solubility. The **simple proteins** are subdivided as follows.

(1) **Scleroproteins** (albuminoids), which are completely insoluble proteins. Examples: keratin (from hair, wool, feathers, horns, etc.), collagen (from skin, tendon), and fibroin (from silk).

(2) **Albumins**, which are water-soluble proteins. Examples: ovalbumin (egg albumin), serum albumin, and lactalbumin (from milk).

(3) **Globulins**, which are proteins soluble in dilute aqueous solutions of salts, in acids and alkalis. Examples: serum globulin, ovoglobulin (from egg yolk), edestin (from hemp seed), and fibrinogen (from blood).

(4) **Glutelins**, which are related to globulins and which are soluble in acids and alkalis but insoluble in salt solutions. Example: glutenin (from wheat).

(5) **Prolamins**, which are soluble in 70 per cent alcohol. Examples: gliadin (from wheat), and zein (from maize).

(6) **Histones**, basic proteins which dissolve in water, giving an alkaline reaction. Example: the histone of the thymus gland.

(7) **Protamins**, strongly basic proteins (simpler than the proteins included in the preceding groups) which, like histones, are soluble in water and give an alkaline reaction. Examples: salmine (from salmon) and clupein (from herring).

The **conjugated proteins** contain the protein molecule united to a non-protein group known as the **prosthetic group** which can often be separated from the protein by hydrolysis.

(1) **Phosphoproteins** in which the prosthetic group is phosphoric acid present in the form of the ester (example: casein from milk).

(2) **Glycoproteins** or **mucoproteins** in which the prosthetic group is a carbohydrate group other than a nucleic acid (example: mucin).

(3) **Lipoproteins** (Volume I, page 416) in which a protein molecule is linked to a lipid.

(4) **Chromoproteins** with a heterocyclic metal-containing (porphin) prosthetic group (example: hemoglobin).

(5) **Nucleoproteins** in which the prosthetic group is a high-molecular-weight nucleic acid (page 427).

Like polypeptides, proteins are amphoteric: they move to the cathode in acid solution and to the anode in alkaline solution. The **isoelectric point** is the pH characteristic for each individual protein, at which the protein does not migrate either to the cathode or to the anode and, hence, its molecule is entirely electrically neutral (exists as the zwitterion).

What is the feature common to all these substances which resemble so little one another in external appearance and in physiological function?

It was found at the beginning of last century that all proteins are related not only by the qualitative but also by the quantitative composition, namely, they contain 50-52 per cent of carbon, 15-18 per cent of nitrogen, 6.8-7.7 per cent of hydrogen, about 24 per cent of oxygen, 0.5-2.0 per cent of sulphur. They also contain a small amount of phosphorus in the form of H_3PO_4 (conjugated proteins), halogens,

metals. Proteins have free carboxyl and/or amino groups and are therefore amphoteric (usually, with the predominance of acid or basic character, depending on whether there are more COOH or NH_2 groups in the molecule). Therefore, proteins are soluble in acids and alkalis too. A number of colour reactions (tests) for detection of proteins have been discovered, which were historically of great importance. Some of these reactions were common to all proteins (or peptides), for example, the **biuret reaction** (in which proteins give a violet or pink colour when treated with an alkaline solution of divalent copper), the **ninhydrin reaction** (which are characteristic of amino acids and which involve the formation of a violet colour on treatment of a mixture containing α-amino acids with ninhydrin—triketohydrindane hydrate). Other colour reactions are characteristic of individual amino acids entering into the composition of proteins (e.g., the xanthoproteic reaction in which proteins produce a yellow colour on treatment with concentrated nitric acid; the reaction depends on the presence of tyrosine).

As early as 1820 it was found that proteins are hydrolysable, and Henri Braconnot isolated the simplest α-amino acid, α-aminoacetic acid, from a protein hydrolysate (it was obtained from gelatine, i.e., from the protein glue of bones, and had a sweet taste and therefore Braconnot called it glycocoll; later it was given the name glycine). In the following decades, other amino acids were isolated from protein hydrolysates, and the discovery of more exotic amino acids continued up to the middle of this century. In the nineties of last century Emil Fischer developed a method of investigating the amino-acid composition of protein hydrolysates. The Fischer method consists in the following: a mixture of amino acids resulting from hydrolysis by means of concentrated hydrochloric acid, is converted by esterification with ethanol and HCl into the esters of amino acids, following which the HCl linked in a salt-like fashion is removed by addition of alkaline and the esters are separated by fractional distillation in vacuum. This preparative method, despite the fact that it was far from perfect (from one-third to half of the entire mass of the amino acids was lost), was a big step forward. It was soon established that the overwhelming majority of proteins that had been investigated contains all or only some of the L-α-amino acids listed in Table 23.1, and only a few proteins contain other amino acids in addition to those presented. The **essential amino acids** (i.e., amino acids that must be included in the human and animal diet) are printed in boldface type in Table 23.1. The total dose of these acids per day is 21-31 g. The other amino acids can be produced by the organism provided that a source of nitrogen is supplied in the food (e.g., in the form of glutamic acid). The amount of these amino acids required for man is 49-51 g per day, i.e., the total amount of amino acids is 70-80 g per day (according to A. A. Pokrovsky).

TABLE 23.1. **The Most Important Amino Acids of Proteins** (the essential amino acids are in boldface type)

Trivial name	Abbreviation	Formula	m. p., °C	$[\alpha]_D$ in glacial acetic acid, degrees	Isoelectric point, pH	Solubility in water at 25°C, g/100 g	Daily dose of amino acids for adults, g
Glycocoll (glycine)	Gly	H_2N-CH_2-COOH	292	—	5.97	25	3
Alanine	Ala	$CH_3CH(NH_2)-COOH$	297	+33	6.00	16.6	3
Valine	Val	$(CH_3)_2CHCH(NH_2)-COOH$	315	+62	5.96	8.85	4
Leucine	Leu	$(CH_3)_2CHCH_2CH(NH_2)-COOH$	337	+22.5	5.98	2.2	4-6
Isoleucine	Ileu	$C_2H_5CH(CH_3)CH(NH_2)-COOH$	284	+49	6.02	4.12	3-4
Aspartic acid	Asp	$HOOCCH_2CH(NH_2)-COOH$	270	+25.4	2.77	0.5	6
Asparagine	NH_2 | Asp (or Asn)	$H_2N-C(=O)-CH_2CH(NH_2)-COOH$	236	+34.3	5.41	2.5	—
Glutamic acid	Glu	$HOOC-(CH_2)_2CH(NH_2)-COOH$	249	+31.8	3.22	0.84	16
Glutamine	NH_2 | Glu (or Gln)	$H_2NC(=O)-(CH_2)_2CH(NH_2)-COOH$	185	+6.1 (in H_2O)	5.65	4.2	—

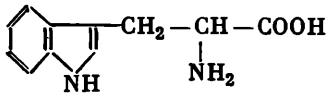
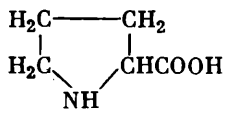
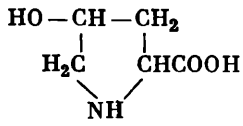
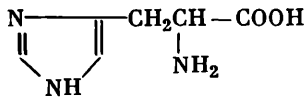
Ornithine*	Orn	$H_2N(CH_2)_3CH(NH_2)COOH$	—	—	—	—	—
Lysine	Lys	$H_2N(CH_2)_4CH(NH_2)COOH$	—	+25.9	9.74	Dissolves well	3-5
Arginine	Arg	$H_2N-C(=NH)-NH(CH_2)_3CH(NH_2)COOH$	238	+29.4	10.76	15	6
Serine	Ser	$HOCH_2CH(NH_2)COOH$	228	+15	5.68	5	3
Threonine	Thr	$CH_3CH(OH)CH(NH_2)COOH$	253	−30	6.16	20.5	2-3
Cysteine	Cys (or CySH)	$HS-CH_2CH(NH_2)COOH$	178	+13	5.02	Dissolves well	2-3
Cystine	CySSCy	$[-S-CH_2CH(NH_2)COOH]_2$	260	−23.2	5.03	0.011	—
Methionine	Met	$CH_3SCH_2CH_2CH(NH_2)COOH$	283	+20	5.74	3.5	2-4
Phenylalanine	Phe	$C_6H_5CH_2CH(NH_2)COOH$	—	−7.5	3.0	—	2-4
Tyrosine	Tyr	$p\text{-}HOC_6H_4CH_2CH(NH_2)COOH$	344	−10	5.66	—	3-4
Tryptophan	Try		382	−34	5.89	1.14	1

Table 23.1, continued

Trivial name	Abbreviation	Formula	m. p., °C	$[\alpha]_D$ in glacial acetic acid, degrees	Isoelectric point, pH	Solubility in water at 25°C, g/100 g	Daily dose of amino acids for adults, g
Proline	Pro		299	−80	6.30	16.2	5
Hydroxyproline	Hypro		270	−77	5.83	36.1	—
Histidine	His		277	+7.5	7.6	4.3	2

* Formed in hydrolysates due to the hydrolysis of arginine.

Proteins are entirely hydrolysed to amino acids with concentrated HCl or with 2-percent HCl on heating in an autoclave; conjugated proteins when hydrolysed lose, in addition, their prosthetic group which is also capable of undergoing hydrolysis in many cases. Emil Fischer and Hofmeister independently came to the conclusion that the amino-acid residues in proteins are linked to one another by the peptide bond (—NH·CO—) (Volume II, page 179). Fischer worked out synthetical methods (1903) of building up polypeptides and synthesized his famous octadecapeptide consisting of 18 amino-acid residues joined in a linear fashion by peptide (amide) linkages. The polypeptides synthesized from L-α-amino acids were found to be similar to the simplest proteins and to **peptones** which are fragments of protein molecules formed as a result of digestion in the stomach. In particular, they are able to decompose hydrolytically under the action of the corresponding enzymes of the digestive tract.

Thus, the theory of the structure of proteins as polypeptides, which was substantiated by E: Fischer, formed a firm basis for investigation of proteins. The problem that remained unsolved was to account for the very diverse physical and biochemical properties displayed by the various proteins of closely related structures. In the twenties of this century, the conceptions of high-molecular-weight compounds (natural rubber, cellulose, starch) were developed. At the same time methods were devised for determination of the molecular weight of high-molecular-weight compounds and, in particular, proteins. The minimum molecular weight of conjugated proteins was formerly deduced from the content of prosthetic groups (or any specific atoms of these groups, say, the iron atom in hemoglobin) proceeding from the assumption that one molecule of a conjugated protein contains one prosthetic group. Even when determined in this way, the molecular weights proved to be very high, say, the molecular weight of hemoglobin was found to be 68,000. The use of the osmotic pressure method for molecular weight determinations (Sorensen, 1917) and, especially, the development of the ultracentrifuge method (Svedberg, 1926) made it possible to carry out a systematic study of the molecular weights of soluble proteins. The molecular weights recorded vary considerably for the individual proteins, ranging from 10,000 downwards for the series of enzymes and hormones (6500 for insulin) to 6,600,000 (the snail hemocyanin) and even to 320,000,000 (the influenza virus protein). If the average molecular weight of the amino-acid residue present in the polypeptide chain of a protein is assumed to be equal to 115, then the number of amino-acid residues in protein molecules will be found to range from several tens to a few millions. Thus, even with respect to molecular weights proteins constitute a class of enormously diverse compounds. The simplest proteins can hardly be regarded as high-molecular-weight compounds, whereas some proteins belong to the class of high-molecu-

lar-weight compounds with the bulkiest molecules. The fundamental difference between proteins as high-molecular-weight compounds and synthetic polymers, such as nylon and polystyrene, and natural high-molecular-weight compounds, such as natural rubber, cellulose, starch, is the large variety of repeating units ("monomers"), of which proteins are composed. Instead of one "monomer" (e.g., the residue of ω-aminocaproic acid or glucose, styrene, isoprene), more than 20 various amino-acid residues are contained in proteins. This was both encouraging and distressing. If the molecule consists of 20 various amino-acid residues, it may have 2,432,902,008,178,640,000 isomers! And if the molecule is assumed to consist of 1000 amino-acid residues, then 20 amino acids can be arranged in this molecule by 20^{1000} ways. This isomerism alone allows not only each species and each individual of the living world but also each cell to have its own characteristic protein. Such an immense variety of possibilities must have bewildered the organic chemist. Let us recall, however, that the possibilities of isomerism, say, in the chemistry of unsaturated hydrocarbons, though incomparably more limited, nevertheless far exceed the feasibility of synthesis of all isomers even for the first ten homologues of methane. Since this circumstance does not confuse the research chemist, the situation with proteins will not seem so hopeless. As a matter of fact, the chemist is not concerned with the synthesis of all isomers possible. What is actually the topic problem in science is the elucidation of the structure of proteins that are the most important from this or that (usually, physiological) point of view, and their synthesis, which is a difficult but quite feasible task, as evidenced by the present status of science.

23.1. Isolation and Purification of Proteins

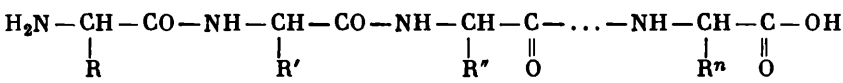
Insoluble proteins have to be simply separated by a series of solvents from all the soluble impurities, which however does not ensure their isolation in the pure state. Soluble (in water, salt solutions, etc.) proteins isolated from cells after their mechanical destruction are subjected to dialysis by placing them in semipermeable (say, cellophane) bags and immersing in water. All electrolytes and low-molecular-weight compounds diffuse through the semipermeable film. This is followed by the fractional precipitation of a mixture of soluble proteins by gradual addition of ethanol or salts [e.g., $(NH_4)_2SO_4$] and chromatography. A more up-to-date method of separation makes use of ion-exchange columns (with sulphonated polystyrene) and molecular sieves of the Sephadex type (from dextrans, see Volume II, page 155).

That the precipitated fractions are individual compounds is confirmed with the aid of paper chromatography or electrophoresis. Many of the proteins can be obtained in the crystalline state after their purification if the solvent is gradually evaporated (say, if the dilute aqueous solution of the salt is evaporated). These methods enable the research chemist to prepare as pure and individual proteins as in the case of all other organic compounds the chemist is dealing with.

Methods of ultracentrifugal fractionation of protein solutions show that, though there exist polydisperse proteins which are mixtures of polymer-homologues of different molecular weights (e.g., gelatine has a molecular weight of 12,000 to 70,000), proteins are generally monodisperse and, in contrast to cellulose, starch and synthetic polymers, are chemically individual compounds rather than mixtures of polymer-homologues (Svedberg).

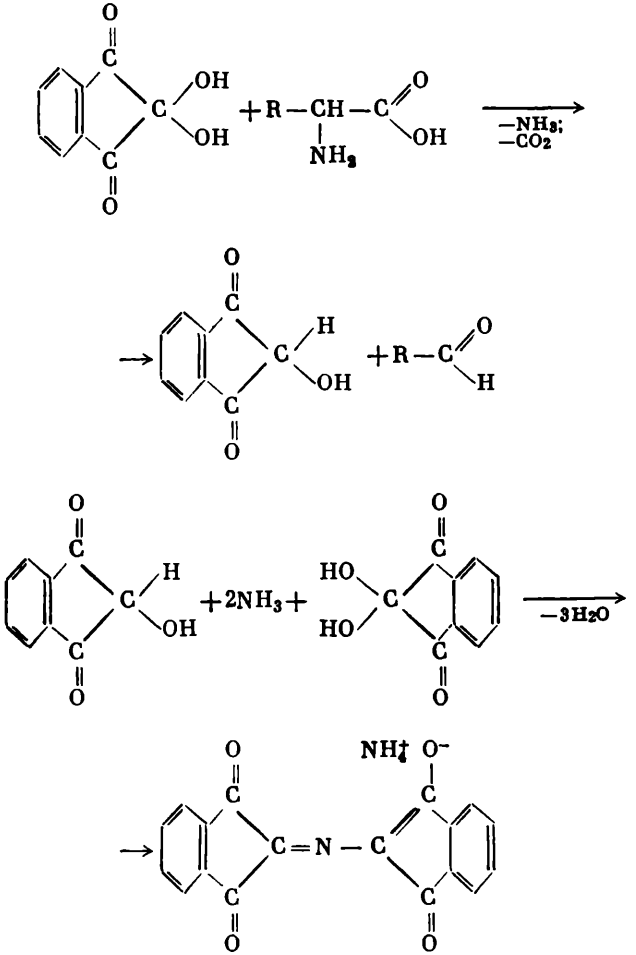
23.2. Elucidation of Protein Structure

The polypeptide chain of proteins has, in a general form, the following structure:



The first question that arises is: What is the total amino-acid composition of a given protein? The technique of determination of this amino-acid composition has been greatly perfected since the time of Emil Fischer with respect to accuracy (which is now 99 per cent) and the speed of operation. After the acid or alkaline hydrolysis (the acid hydrolysis destroys tryptophan and the two methods of splitting have to be combined) a solution of a mixture of amino acids is passed at pH 2 through an ion-exchange resin (sulphonated polystyrene in the form of a sodium salt) which binds all the amino acids due to their ammonium function, and is then gradually eluted by acid buffer solutions with pH increasing from 3.5 to 5.5 and further to 11, i.e., they become increasingly less acidic. The amino acids are eluted in order of decreasing acidity; at the end, with a buffer of pH 11, the diamino acids are eluted. At present, all separating operations are accomplished by means of automatic analysers, in which the change of buffer solutions is effected automatically, and the number of isolated amino acids is determined photometrically by the intensity of the blue-violet coloration arising in the reaction with ninhydrin, which forms the same dye with all amino acids as

a result of the following reactions:

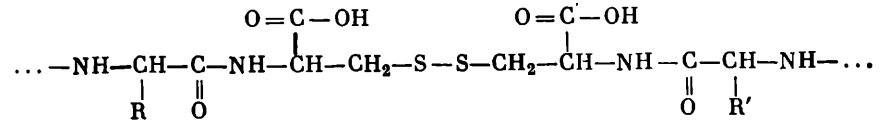


The readings of the photocell are graduated by the spots formed by known amounts of amino acids. Exceptions are proline and hydroxyproline which give a yellow colour under these conditions.

The analysis of amino acids by means of the Moore-Stein-Spackman automatic amino-acid analyser takes only a few hours. But this analysis does not provide information on the order in which the amino acids occur in the molecule (the **amino-acid sequence**).

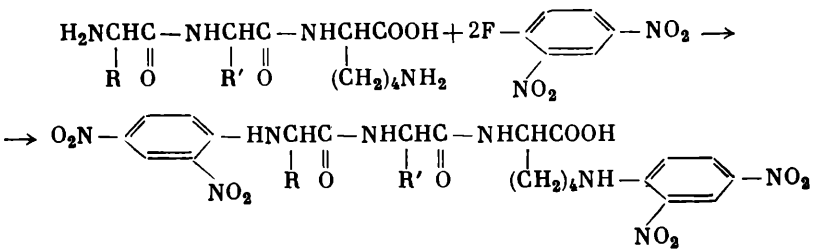
There are several methods for establishing the amino-acid sequence in the molecule:

1. In many proteins, the individual portions of the molecule have been found to be linked by disulphide bridges due to cystine:

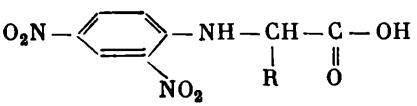


By oxidizing the sulphur to the $-SO_3H$ group, it is possible to break up the molecule into portions at the —S—S— linkages. The same can be achieved by reducing the —S—S— bridge to two mercapto groups, —SH and HS—, for example, by the action of $HSCH_2COOH$ which is oxidized to $(-S-CH_2-COOH)_2$ or with the aid of mercaptoethanol, $HSCH_2CH_2OH$.

2. By reacting the protein with 2,4-dinitrofluorobenzene, which is an active electrophilic reagent (with a "mobile fluorine") it is possible to dinitrophenylate the free amino groups of the protein. These may be amino groups of two types: the secondary amino groups of diamino acids, such as lysine, or terminal amino groups. For example:



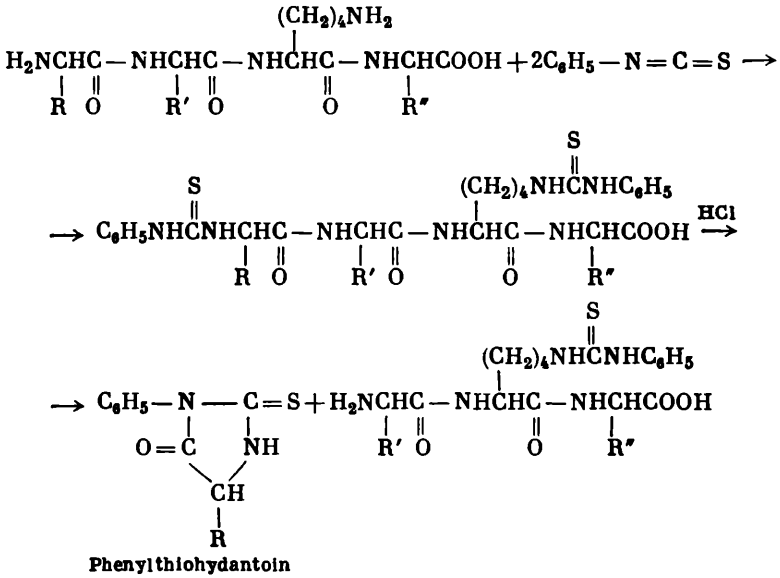
Cautious hydrolysis eliminates the 2,4-dinitrophenylated amino acid written on the left in the scheme:



After this dinitrophenylamino acid is separated and identified, say, by paper chromatography, it is possible to determine one of the terminal amino acids in the protein molecule, which is called the N-terminal amino acid (Sanger's method, 1949). This method has a disadvantage: under the conditions of acid hydrolysis the dinitrophenyl derivatives of glycine, cystine, proline, and tryptophan are destroyed.

Another method of terminal group analysis is that of P. Edman (1949) in which the protein is treated with phenylisothiocyanate which unites with a free amino group of terminal amino acids to form phenylthioureas. When such a phenylthiourea is treated with dilute hydrochloric acid in nitromethane, the amino-acid residue, in

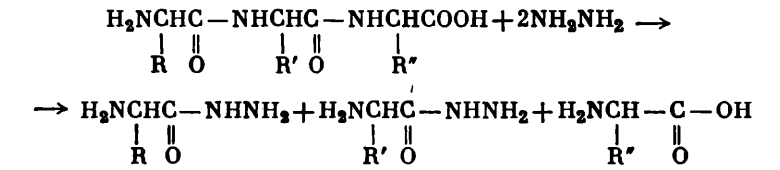
which the phenylthiourea grouping is in the α-position, is easily eliminated since on being removed it leaves a stable five-membered heterocycle—phenylthiohydantoin:



Phenylthiohydantoin

Using this method, one can, step by step, cut off one amino-acid residue at a time from the N-terminal amino acid. For example, Fraenkel-Conrat succeeded in determining the sequence of the first eight amino acids in the adrenocorticotropic hormone.

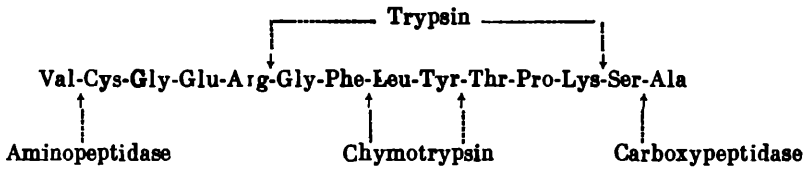
3. For splitting-off of amino-acid residues from the C-terminal amino acids (i.e., amino-acid residues bearing a free carboxyl group) Akabori proposed the use of hydrazine (at 100°C for a few hours). The reaction may be formulated thus:



From the scheme it is seen that the entire chain breaks down into the hydrazides of amino acids, except the first (from the C-terminal) amino acid which is isolated in the free state. After the resulting mixture is treated with a suitable aldehyde, which binds the hydrazides into sparingly soluble hydrazones the free amino acid is isolated chromatographically.

4. The C-terminal amino acids can most simply be eliminated by enzymatic hydrolysis. For instance, the enzyme carboxypeptidase (from the pancreas) successively splits off amino acids containing a carboxyl group. A disadvantage of this method is that proline and hydroxyproline are not eliminated by carboxypeptidase.

Of course, a series of successive eliminations can much more simply be applied to polypeptides with a small number of amino-acid residues than to proteins of complex structure. In the case of complex proteins, use is made of the fact that under different conditions hydrolysis cleaves them at different linkages and, hence, gives different sets of lower-molecular-weight polypeptides. On hydrolysis with dilute acids, the linkages of dibasic amino acids are first broken; under the action of concentrated acids the linkages of hydroxyamino acids are first cleaved, and on alkaline hydrolysis the bonds of threonine are disrupted. The digestion enzyme, trypsin, attacks the peptide linkages of lysine and arginine with the amino groups of other amino acids; chymotrypsin breaks the bonds of aromatic amino acids; carboxypeptidase, as has already been said, splits off C-terminal amino acids with a free carboxyl group; and aminopeptidase splits off N-terminal amino acids with a free α-NH_2 group. What has been said is illustrated by the following scheme:



As a result of hydrolysis under different conditions, there is produced a set of polypeptide fragments which are separated by the chromatographic methods developed by Martin and Synge. These methods are paper chromatography, partition chromatography, and also electrophoresis. The sequence of amino acids in each of the polypeptide fragments can be established by means of the methods described above, say, by the Edman method. Comparing the amino-acid sequences in the fragments and taking into account that in some of the fragments there is an overlap (they contain the amino-acid sequence of the end of the first and the beginning of the second of a pair of fragments), it is possible to establish the total amino-acid sequence in the polypeptide chain. As an example, let us designate individual amino-acid residues by letters. If after hydrolysis we identify the following series of polypeptide fragments

ACEB
EBD
BDAI
DA
IJ

then it will be clear that the amino-acid sequence in the parent polypeptide was ACEBDAIJ.

5. A promising mass-spectrometric method has recently been developed by M. M. Shemyakin, M. N. Kolossov, and N. S. Vul'fson and also by Lederer for determination of the amino-acid sequence in polypeptides, which has already been described (see Volume II,

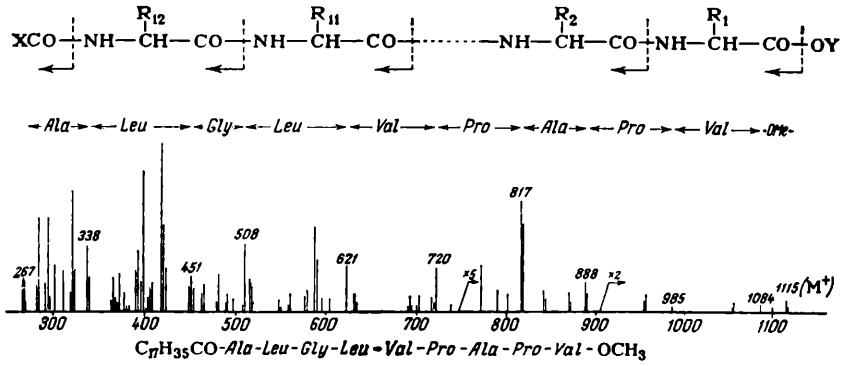


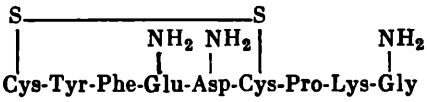
Fig. 23.1.

The mass-spectrogram of N-acylated methyl ester of nonapeptide (M. M. Shemyakin, M. N. Kolossov, N. S. Vul'fson).

page 155). Recall that the polypeptide acylated at a free amino group (the N-terminal on the left) and esterified at a free carboxyl group (the right end) first loses the alkoxyl group (OY) in the mass-spectrometer and forms a cation with the positive charge on the $-\overset{+}{C}=O$ end of the molecule. This is followed by the successive eliminations of amino-acid residues from right to left, as a result of which increasingly lighter fragments are obtained (amino-acid residues are removed one at a time, in the order of arrangement, from right to left)—cations with the positive charge on the $-\overset{+}{C}=O$ end. Comparing the molecular weights of a series of residues one can find out which amino-acid residues were split off each time and establish their sequence. This is illustrated in Fig. 23.1, where X—CO— denotes stearoyl and Y = methyl.

An example of a simple natural polypeptide, the antibiotic Gramicidin S, was given in Volume II, page 186. Below are given examples of sufficiently complex proteins, whose structures were established in the period 1945-1965 by the methods described earlier.

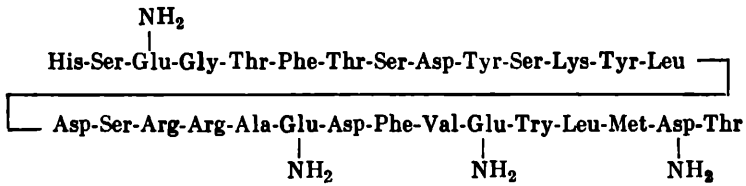
Hormones:



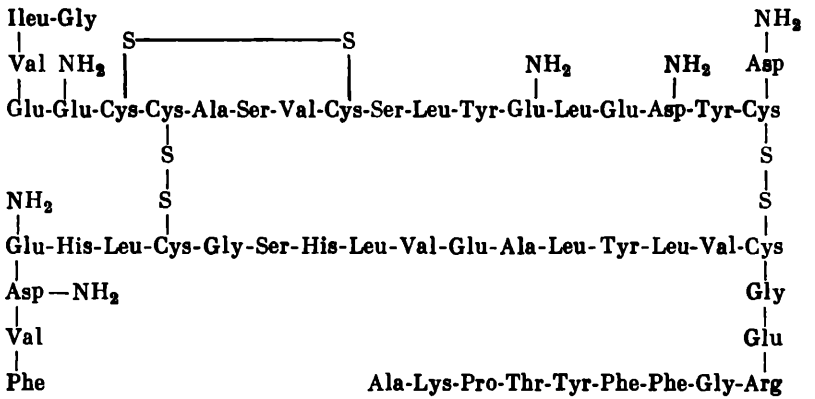
Pig vasopressin

H_2N-Asp-Arg-Val-Tyr-Ileu-His-Pro-Phe-His-Leu-COOH

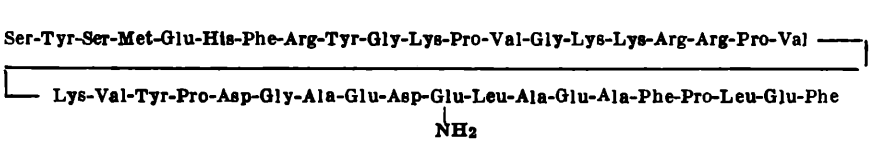
Horse hypertensin (renin)



Glucagon



Steer insulin (the pancreas hormone)



Adrenocorticotropic hormone (ACTH)

The formula of the protein of the tobacco mosaic virus is as follows:

The protein of the tobacco mosaic virus

23.3. Synthesis of Peptides and Proteins

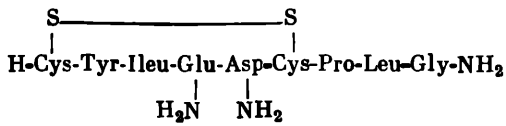
The principles underlying the synthesis of peptides have already been discussed (see Volume II, Section 4.6). The synthesis of proteins, the structure of which (the amino-acid sequence) is known, differs from that of peptides only by the immensity of the task.

Apart from the methods described above, tosylation is also used to protect the amino group, which involves the action of *p*-toluenesulphochloride. The tosyl group (*p*-toluenesulphonyl) is removed by reduction with metallic sodium in liquid ammonia. The same method is used to remove the carbobenzoxy group, which (and this is especially important) can also be removed by catalytic hydrogenation.

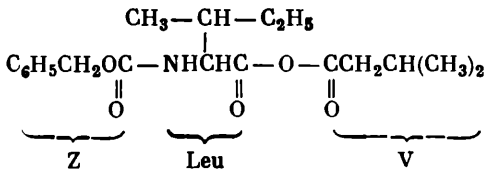
The mercapto (thiol) group can be protected by benzylation, and removal of the benzyl group is achieved by the action of sodium in liquid ammonia.

The acylation of a peptide with other amino groups being protected is accomplished (apart from the methods mentioned in Volume II) also by the action of mixed anhydrides, such as the mixed anhydride of a given amino acid and isovaleric acid. No less popular is the method involving the action of one amino acid (or a polypeptide with protected amino groups) on another in the presence of the ester of pyrophosphorous acid or the above-mentioned dicyclohexylcarbodiimide. Some cases of the application of such procedures will be considered below.

We shall cite, as an example, the synthesis of the hormone oxytocin accomplished by du Vigneaud. This hormone secreted by the posterior lobe of the pituitary has a relatively simple structure:

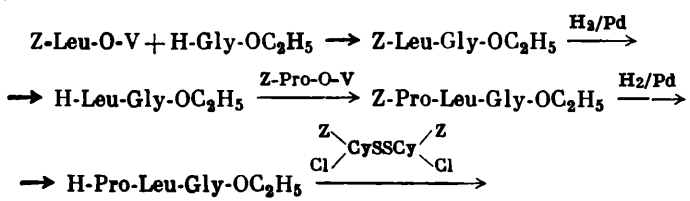


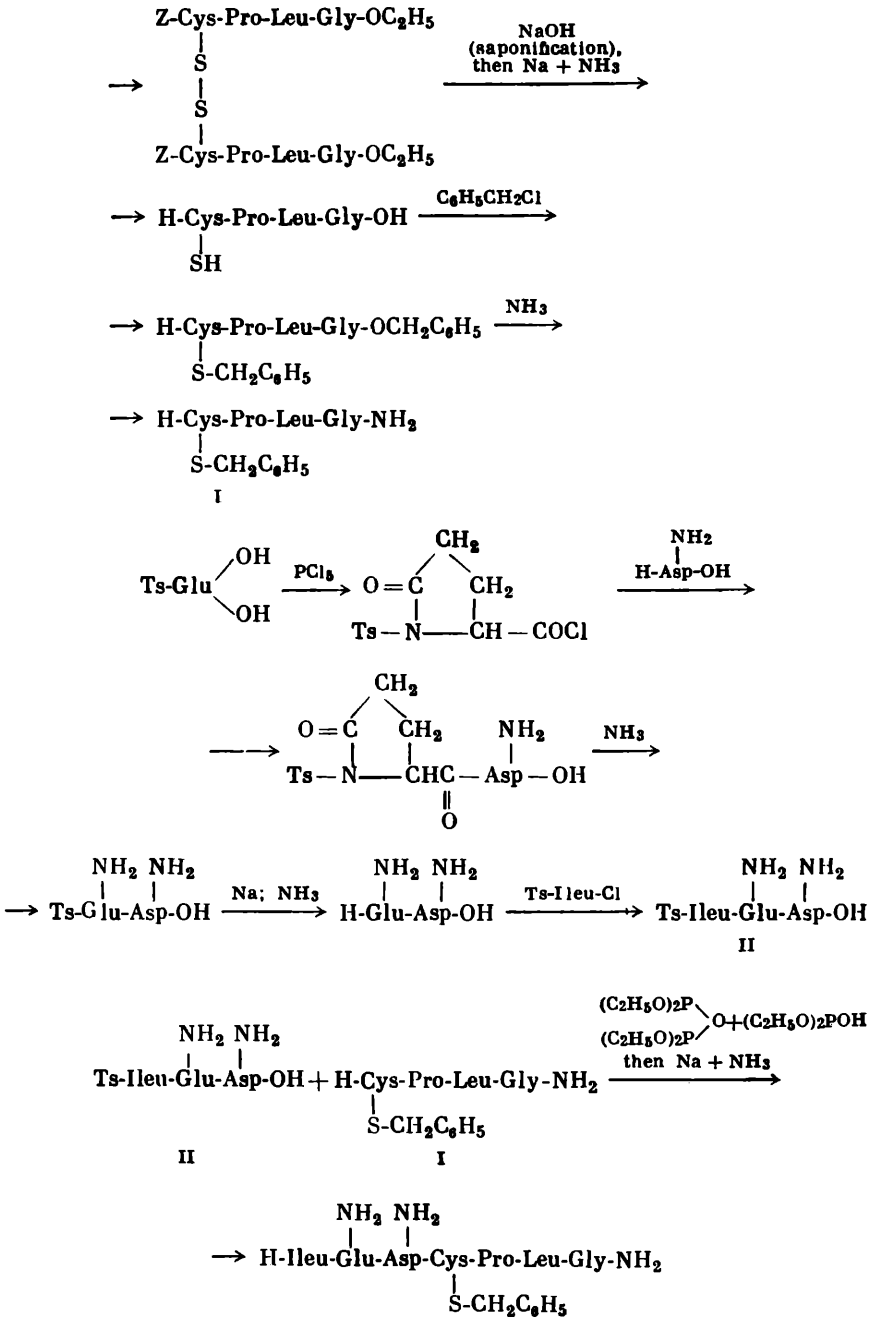
Hereafter the isovaleric acid residue in mixed anhydrides of amino acids and this acid will be denoted, for the sake of brevity, by the letter V, and the carbobenzyloxy group, $C_6H_5CH_2$—OCO—, will be designated by the letter Z; the tosyl group is denoted as Ts, as usual, so that the formula of the mixed anhydride of isovaleric acid and carbobenzoxylleucine, which has the form

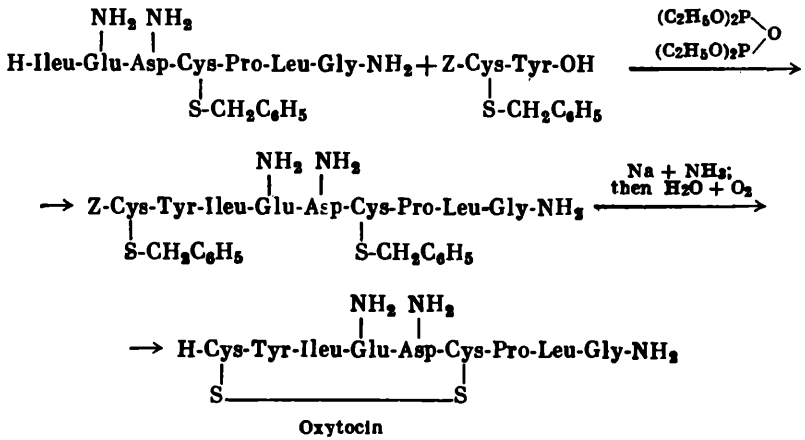


will look like Z—Leu—O—V.

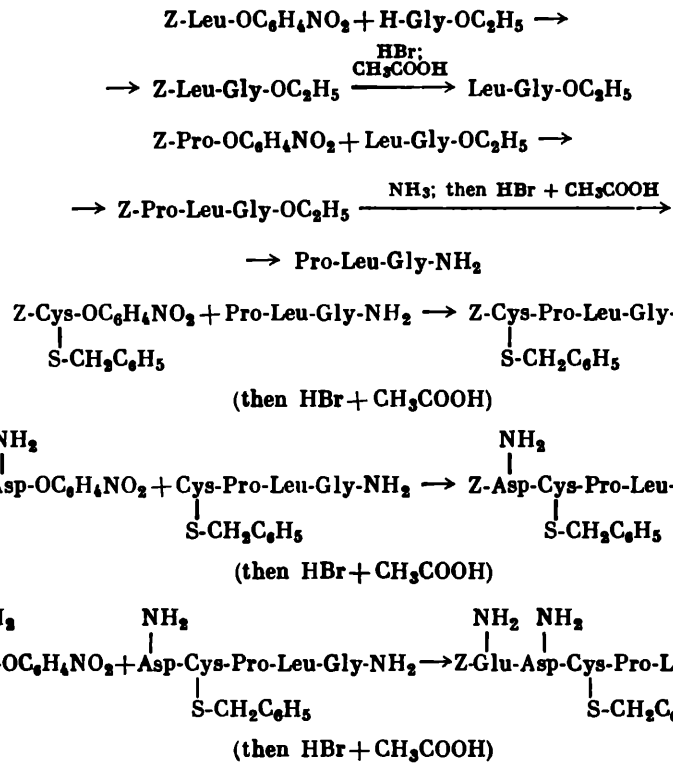
The first phase of the synthesis is the acylation of the ethyl ester of glycine by the mixed anhydride of isovaleric acid and leucine, which is protected by carbobenzoxylation. Thus, the synthesis begins from the right-hand end of the oxytocin molecule in the above formula:

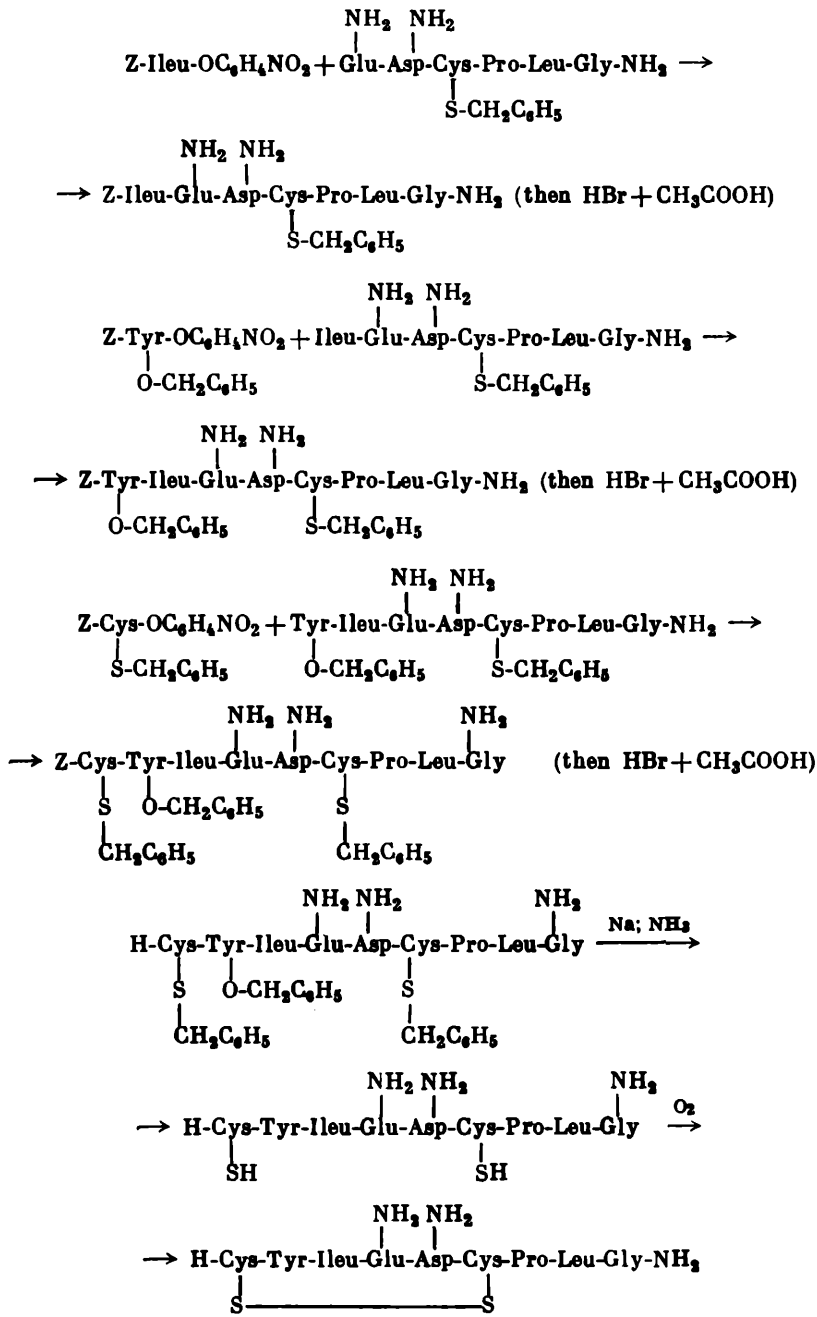



Z-Cys-Pro-Leu-Gly-OC2H5
NaOH (saponification), then Na + NH3
H-Cys-Pro-Leu-Gly-OH
C6H5CH2Cl
H-Cys-Pro-Leu-Gly-OCH2C6H5
NH3
H-Cys-Pro-Leu-Gly-NH2
I
Ts-Glu
PCl5
H-Asp-OH
Ts-Glu-Asp-OH
Na; NH3
H-Glu-Asp-OH
Ts-Ileu-Cl
Ts-Ileu-Glu-Asp-OH
II
(C2H5O)2P
(C2H5O)2POH
Ts-Ileu-Glu-Asp-OH + H-Cys-Pro-Leu-Gly-NH2
then Na + NH3
H-Ileu-Glu-Asp-Cys-Pro-Leu-Gly-NH2



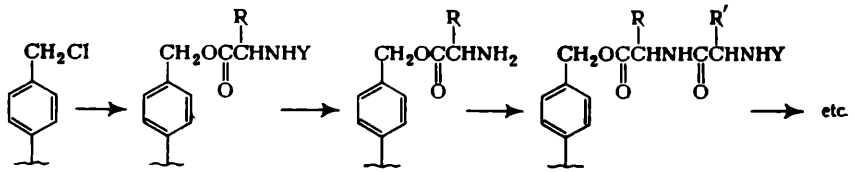
The synthesis of oxytocin carried out later by du Vigneaud and Bodansky is simpler and is as follows:





The protein hormones hypertensin, vasopressin, and adrenocorticotropic hormone (ACTH) synthesized in a manner similar to that of the synthesis of oxytocin have been found to be identical with the natural compounds in all the properties, including the physiological effect.

The American chemist R. B. Merrifield developed a new method of synthesis of polypeptides (the first publication appeared in 1952), which was found later to be extremely promising. In this method, which is called *solid phase peptide synthesis*, use is made of an ion-exchanger on which one amino acid, the first unit of the desired polypeptide, becomes fixed by its carboxyl end. Then the amino group of the first amino acid is acylated by the second amino acid, and so on. Eventually, the resulting polypeptide is separated from the ion-exchanger by the action of acid:



This method makes it possible to provide a good yield of the desired product and to speed up the process considerably.

The important part in the identification of proteins is played by immunological reactions. The foreign protein introduced into the bloodstream of an animal automatically causes the formation of a protein antibody which binds the protein introduced. The antibody is formed from the γ-globulin fraction of the blood proteins. The immunity to a new infection, which is elaborated as a result of some diseases or of inoculation, is based on the generation of antibodies to the given species of bacterial and virus proteins. The antibody also gives the reaction (detected by the eye) with the protein responsible for its formation (the antigen)—the formation of a precipitate on mixing the solutions. Using immunological reactions, one can differentiate between proteins of very closely related structures. Thus, it is possible to differentiate between the human hemoglobin and the steer hemoglobin.

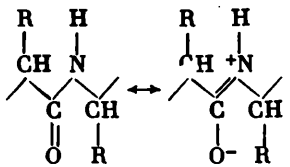
It should be kept in mind that the antigen activity is exhibited not by the entire molecule of the protein introduced but by definite groupings, which are different in different cases. The antigens deliberately introduced into the protein can play the role of such groupings. For instance, the diazotized *p*-aminophenylarsonic acid enter into the azo-coupling reaction with the tyrosine unit of the protein, and the thus modified protein (the horse blood serum) when administered to the rabbit causes the formation of a specific antibody. But this antibody is also effective against the thus treated

serum of other animals. Thus, the possibilities of immunological identification of proteins must not be overestimated. We shall not describe the hypotheses concerning the mechanism of generation of antibodies since no conclusive evidence has been obtained so far.

23.4. The Secondary and Tertiary Structures of Proteins

The sequence of the valence bonds in a peptide taken alone does not yet account for the fundamental differences in the physical properties of various proteins. The X-ray structure analysis of crystalline peptides and stretched strand-like proteins (wool, silk) has led to the following conclusions.

1. In amino-acid residues, the peptide linkage —CO—NH— lies in a single plane, which may be explained by the partial double bond character of the nitrogen atom and, hence, by its partial ammonium character (the presence of a partial positive charge). Thus, the carbonyl group must be "opened" more than usual with the partial negative charge being localized on oxygen. This is confirmed by the decreased C—N distance (1.35 Å instead of 1.47 Å) and the increased C=O bond length (1.28 Å instead of 1.24 Å). Such a planar structure is relatively rigid and is fixed so that the hydrocarbon residues of amino acids are in the *trans*-position relative to one another:



Free rotation about the C—C axes is usually retained.

2. The most essential feature in the structure of peptides, which determines the types of molecular conformations, is the formation of hydrogen bonds, N—H···O=C, either between two different planar chains of the peptide (the β-structure, Fig. 23.2*a*) or between the units of the same peptide chain twisted due to free rotation about the C—C bonds into a spiral coiled about an imaginary cylinder (the coil is referred to as an α-helix, Fig. 23.2*b*).

The α-helix is more stable than any other and more characteristic of proteins. When, for example, hair (keratin) or the spine of the porcupine is stretched, the α-helix changes to the β-structure. Regardless of the size and nature of the amino-acid residues (aromatic, aliphatic, or heterocyclic), the length of one amino-acid residue

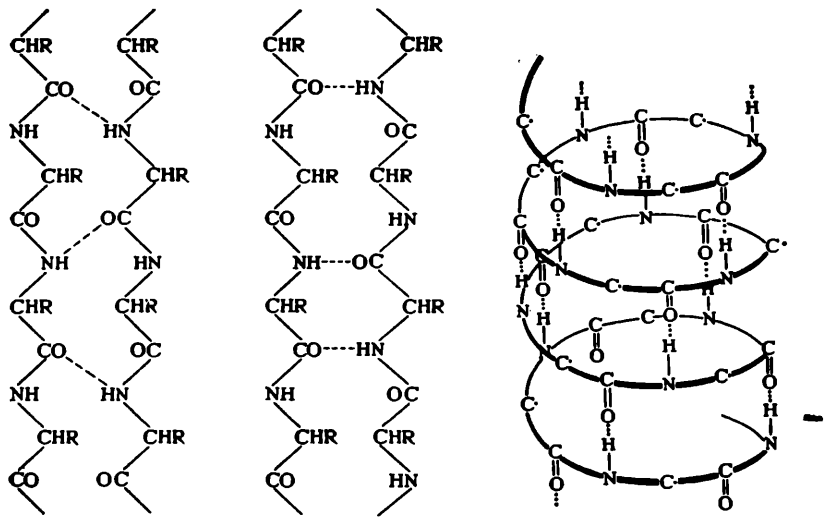
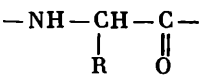


Fig. 23.2.

The structure of the polypeptide chain of protein:
a—the β-conformation with intermolecular hydrogen bonds; *b*—the helical α-conformation of protein with intramolecular hydrogen bonds.



in the α-helix along the cylinder surface is the same (1.5 Å) and the pitch of the helix (the distance between two successive turns) is 5.4 Å, so that there are 3.6 amino-acid residues for each turn of the helix. The hydrogen bonds (*intramolecular* hydrogen bonds) in the α-helix are formed between the hydrogen of the NH group in one turn and the oxygen of the CO group in the next turn (between each first and fourth —CO—NH— groups) along the cylinder generatrix.

In principle, the α- and β-structures are the conformational varieties of peptide chains, which are often called the **secondary structure** of peptides and proteins. These helical models (the α- and β-structures) were proposed by Pauling. Using synthetic polypeptides built up of the residues of one amino acid (e.g., polylysine), it is possible to demonstrate the reversibility of interconversions of the α- and β-conformations of a solid substance as a result of a mechanical action or a change in moisture content. When a synthetic polypeptide (e.g., polyglutamic acid) or a protein is dissolved in water,

the α-helix survives. Only when the temperature is increased, do there take place, within a rather narrow temperature range, "melting"—the breaking of the hydrogen bonds in the α-helix, the formation of new hydrogen bonds with water and the change to the globular structure, which is accompanied by a sharp decrease in the viscosity of the solution. Such a disturbance of α-helical structures also occurs upon dissolution in an aqueous solution of urea (e.g., in 8*M* solution) or in dichloroacetic or trifluoroacetic acid (due to the formation of *intermolecular* hydrogen bonds); dimethyl formamide does not destroy the α-helix. The destruction of α-helical structures and the reverse process, helix formation, can be followed by (1) a change in viscosity; (2) the acceleration or retardation of deuterium exchange; (3) a change in the rotation of the plane of polarization; (4) the optical rotatory dispersion (OPD). Each of these indices also permits of a quantitative interpretation. Let us consider the second and third characteristics.

Linderstrom-Lang suggested that the number of intermolecular hydrogen bonds in a protein be estimated by the rate of deuterium exchange of the group $-\overset{\overset{\|}{O}}{C}-\overset{\overset{|}{H}}{N}-$ at different pH values. The simplest peptides exchange their hydrogen at an immeasurably high velocity. In the α-helix, which contains intermolecular hydrogen bonds, the deutero-exchange in the groups

$$\diagup N-H \cdots O=C\diagdown$$

proceeds for hours. In this way the degree of helix formation (in per cent) can be determined.

The method *3* is based on the following considerations. In principle, the helix of an L-amino-acid polypeptide may be right- or left-handed (the mirror image). From theory it follows that the right-handed helix, regardless of the presence of asymmetric carbon atoms in its units, will rotate the plane of polarization to the right, and this magnitude will be supplemented by the contributions from the asymmetric carbon atoms of each of the L-amino acids; therefore, upon dissolution in a "mild" solvent there is observed the total magnitude of rotation, and in a solvent that destroys the α-helix only the contribution of asymmetric atoms is left.

In synthetic "polymers" of amino acids, only the right-handed helix has been observed up to the present time; the same helical arrangement is typical for proteins, but in this case the left-handed helix is probably also encountered. Thus, by changing the medium it is possible to transform fibrous peptides and proteins (which have long macromolecules and form highly viscous solutions) into globular ones—with a spherical shape of molecules and low viscosity of solutions.

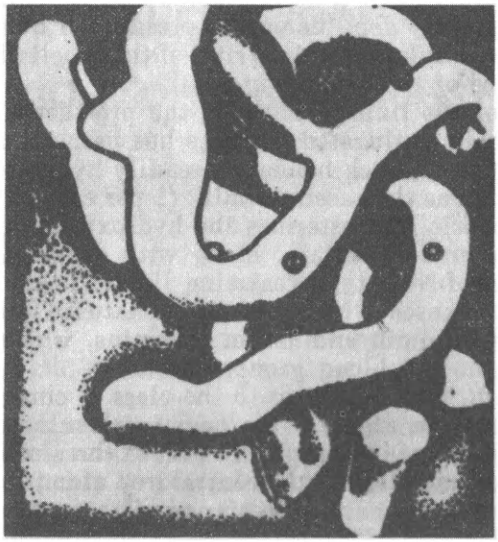


Fig. 23.3.
The tertiary structure of myoglobin.

Some proteins when heated undergo irreversible denaturation, a molecular disorganization. This is a process of "melting" of α-helices followed by a random formation of intermolecular hydrogen bonds and cross-linking of the macromolecules along new directions. Less prone to denaturation are proteins with many "vulcanizing" —S—S bridges, in which case the destruction of the α-helical structure is occasionally reversible since the disulphide bridges impart certain rigidity to the structure.

As shown by the laborious and detailed X-ray studies of comparatively complex proteins, apart from the primary and secondary structures, there also exists the **tertiary structure** which depends on the folding or twisting of helical coils. The idea of the tertiary structure can be ascertained by referring to the Kendrew model of the myoglobin molecule, which has been elucidated through the use of X-ray diffraction studies. In some cases, the tertiary structure (e.g., in keratin or collagen) is made up of several α-helical coils wound together to form the stranded cable structure. In other cases, the tertiary structure results from the nonuniform multiple folding-up or bending of an α-helical coil which is thus intertwined into roughly a sphere, just as in myoglobin (Fig. 23.3) or in ribonuclease. The tertiary structure, as will be shown at a later time in a discussion of the structure of ribonuclease, is also largely due to hydrogen bonds,

but in this case no ideal α-helix is produced. Besides, the tertiary structure also greatly depends on the presence of disulphide cystine bridges that cross-link the various sites of the α-helix brought closely together because of the coil being bent.

The nature of the linkage between the prosthetic group and the protein portion in conjugated proteins has been clarified not in all cases. In many cases, such bonds are readily hydrolysable. In phosphoproteins, such as the casein of milk (1 per cent of P) and the egg vitellin, phosphoric acid esterifies the hydroxyl group of the serine residue. Glycoproteins contain, along with sugars and polysaccharides, molecules of N-acetylhexosamine linked to the protein. These are soluble substances which are not denatured on heating. They include the egg albumin and serum albumins, which, among other things, determine the blood groups.

In hemoglobin, which belongs to the class of chromoproteins, the central divalent iron atom in the haem molecule is linked to the four nitrogen atoms of the porphyrin part of the molecule, which are arranged in the same plane as the central iron atom; above this plane, the water molecule forms the fifth apex of the octahedron, and the sixth apex below the plane is the nitrogen atom of the histidine residue of the protein—the globin. In oxyhemoglobin, the place of the water molecule is occupied by the oxygen molecule (the iron remains divalent, the oxygen is linked by a coordinate bond and dissociates reversibly). When it is poisoned with carbon monoxide, the place of the water or oxygen molecule is taken by the firmly attached carbon monoxide molecule

Chapter 24

Nucleotides and Polynucleotides

24.1. Protein Biosynthesis

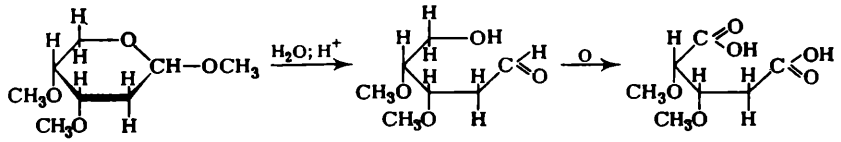
The nucleus of each cell and the cytoplasm contain polynucleotides, high-molecular-weight nucleic acids (from *nucleus*) which are bound with proteins, probably by the salt-like bond and also by hydrogen bonds, into nucleoproteins. In any case, the bond between nucleic acids and protein is easily broken, and then the two components can be separated from each other.

Viruses which have no cellular structure, are also nucleoproteins from the chemical standpoint. The important biological role of nucleic acids in viruses is deduced from the fact that on infection with a virus (say, with a bacteriophage—the bacterial virus) the infected cell acquires only a nucleic acid from the virus, and the protein part (the protein shell) of the virus remains outside, does not enter the cell and is rejected. After the infection, a multitude of virus (bacteriophage) particles are produced inside the host cell due to the nucleotide, amino-acid, and enzyme resources of this cell. These new particles are composed not only of recurring nucleic acids but also of protein shells which are identical with the protein of the original infecting virus particle, though the protein has not entered the infected cell. It thus follows that nucleic acids play the deciding role in protein biosynthesis, further proofs for which will be given at a later time. This has focused attention on polynucleotides; some individual nucleotides have been known since the time of Liebig.

The determination of the molecular weight of nucleic acids (polynucleotides) by the sedimentation method on the ultracentrifuge gives values ranging from 200,000 to several millions. The complete hydrolysis of the nucleic acids of the cell nucleus has revealed the presence of three groups of the constituents of these so-called **desoxyribonucleic acids** (or *deoxyribonucleic acids*, usually abbreviated to DNA). These groups are phosphoric acid, D-2-deoxyribose (i.e., D-ribose, in which the second carbon atom bears a second hydrogen

atom instead of the hydroxyl group; see Volume II, page 130), and a mixture of four heterocycles: two purine bases—adenine and guanine and two pyrimidine bases—thymine and cytosine (see Volume III, pages 409 and 423). The full hydrolysis of the nucleic acids of the **cell plasma**, which are known as **ribonucleic acids** (RNA), also yields phosphoric acid, D-ribose (in place of D-deoxyribose) and a mixture of the same adenine, guanine, cytosine and, in addition, uracil. There is no thymine (the methyl homologue of uracil) present in them.

D-Ribose and D-2-deoxyribose were isolated by P. A. Levene in 1909 from the corresponding nucleic acids after their hydrolysis (in the case of deoxyribonucleic acids, by the action of 0.01*N* HCl for 10 minutes). The structure and configuration of D-ribose has been established on the basis of the identity of its osazone with the osazone of D-arabinose, from which follows the epimerism of these two sugars (see Volume II, page 120). The structure and configuration of D-2-deoxyribose have been proved by the oxidation of a methylated sugar to 1,2-dimethoxyglutaric acid of known configuration:



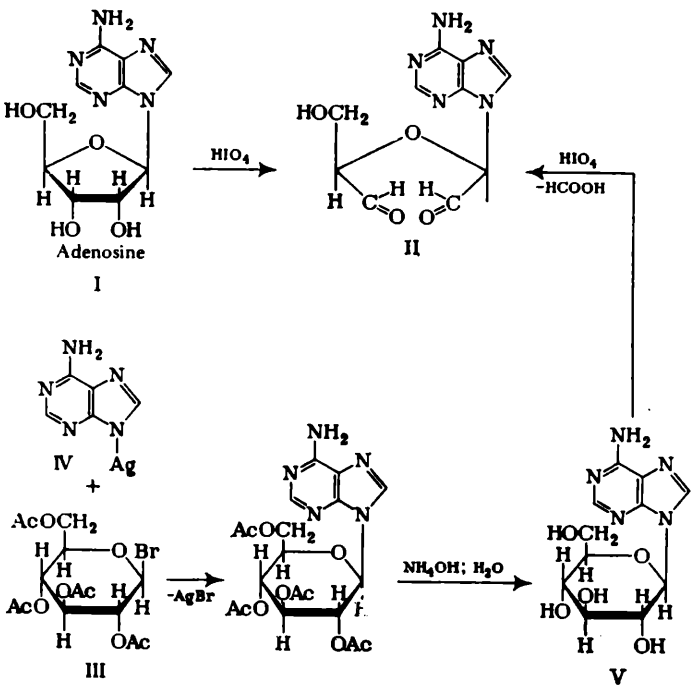
High-molecular-weight polynucleotides can be split into simple nucleotides by the cautious alkaline hydrolysis of ribonucleic acids or by hydrolysis with the aid of enzymes (e.g., ribonuclease for ribonucleic acids; and the phosphodiesterase of snake venom for deoxyribonucleic acids). In the molecule of a simple nucleotide, any of the above-mentioned heterocyclic bases is linked to ribose (to deoxyribose in DNA) and phosphoric acid. which esterifies the sugar portion of the nucleotide. This follows from the fact that a free heterocycle and the isomeric phosphates of D-ribose (and, accordingly, of D-2-deoxyribose) can be found among the products of the hydrolysis conducted under appropriate conditions. On the other hand, the hydrolysis of nucleic acids or isolated nucleotides can be made (enzymatically or by the action of ammonia) to yield the corresponding **nucleosides**, i.e., it is possible to split off phosphoric acid, leaving the heterocycle and sugar bound together. Thus, nucleotides—"monomers", the polycondensation of which (with elimination of water) gives polynucleotides ("polymers")—are the phosphoric esters (phosphates) of the nucleosides. Since the hydrolysis products of nucleosides—pyrimidine and purine heterocyclic bases (and also ribose or deoxyribose)—are identified by comparing with known specimens, the problem that remains to be solved is to locate the point of attachment of the heterocycle to the sugar, the mode of their cyclization, the configuration of the glycoside centre and, finally,

the site of phosphorylation of the carbohydrate portion of the molecule of both types of nucleic acids.

That the heterocycle-sugar linkage is difficult to hydrolyse indicates that this is neither the C—C bond (non-hydrolysable) nor the C—O bond (readily hydrolysable). Thus, the only linkage possible is the C—N bond. As might be expected, this bond involves the "aldehyde" carbon atom (C-1) on the part of the sugar. This is proved, in particular, by the series of reactions carried out by Todd who used adenosine I, which on oxidation with periodic acid forms a dialdehyde II. This dialdehyde is identical with the dialdehyde resulting from the periodate oxidation* of the saponified N-glucoside V synthesized by the interaction of tetraacetylbromoglucose III with the silver salt of adenine IV (see the scheme shown below).

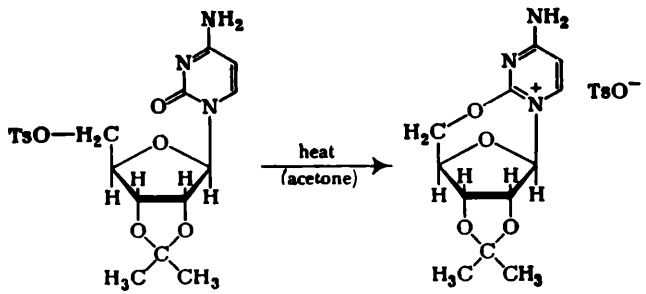
The synthesis of V from tetraacetylbromoglucose proves the glycoside character of the linkage of glucose in compound V, and the identity of the oxidation products of I and V establishes the glycoside character of the bond in adenosine. At the same time, since in the derivative of V the configuration of the first atom of glucose is β-glycosidic, adenosine is also found to have the β-glycosidic configuration.

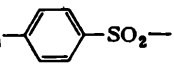
The structure of adenosine is proved as follows:



* For oxidation with HIO_4, see Volume II, page 125.

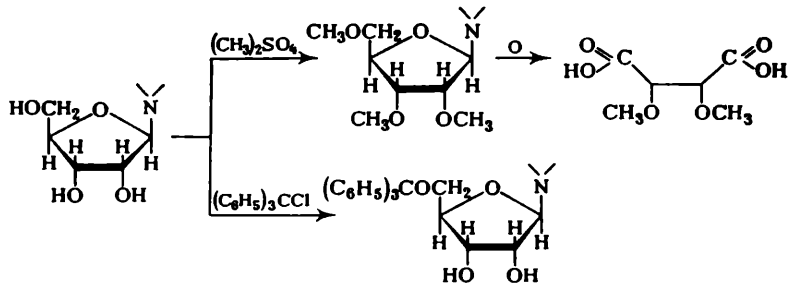
The β-configuration of the glycosidic centre is confirmed even more conclusively by the easy formation of cyclonucleosides. The intramolecular cyclization of 5′-tosyl-3′-acetyldeoxyadenosine, 5′-tosyl-2′,3′-isopropylidenecytidine and other analogous derivatives may occur only if the parent glycoside is a β-glycoside (in this case, the CH_2OH group and the heterocycle are on the same side of the sugar ring). In the example given, cyclization takes place due to atoms 2,5′:



where TsO= 

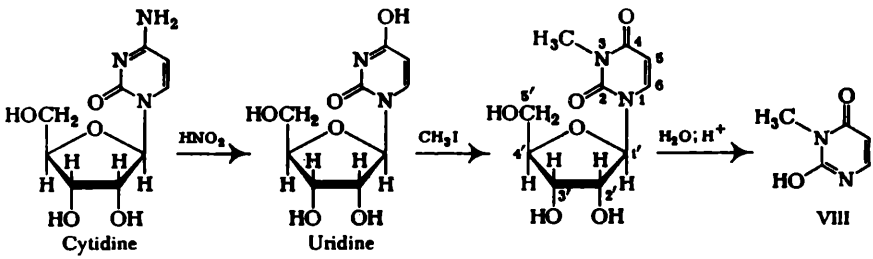
In the case of 5′-tosyl-3′-acetyldeoxyadenosine, cyclization occurs due to atoms 3,5′.

The ribose of nucleotides has the furanoside structure (a five-membered ring), as has been proved by the oxidation of their methyl O-esters, which gives only dimethoxysuccinic acid. This is supported by the fact of formation of trityl (triphenylmethyl) esters of ribonucleotides and deoxyribonucleotides (triphenylchloromethane is known to alkylate only the primary and not the secondary hydroxyl of alcohols).



But which of the nitrogen atoms of pyrimidine and purine heterocycles is linked to the glycoside carbon atom? As regards the pyrimidine nucleotides, this cannot be the nitrogen of the amino group of cytidine since when cytidine VI is reacted with nitrous acid, its

amino group is replaced by a hydroxyl group and it is converted into uridine VII without loss of the bond with the sugar. This reaction also indicates that in uridine and cytidine the bond with ribose is formed via the same nitrogen atom. If uridine VII is methylated with methyl iodide, then the subsequent hydrolysis with elimination of ribose will yield 3-methyluracil VIII (the numbering of atoms in methyluracil has been approved by UPAC in 1968):



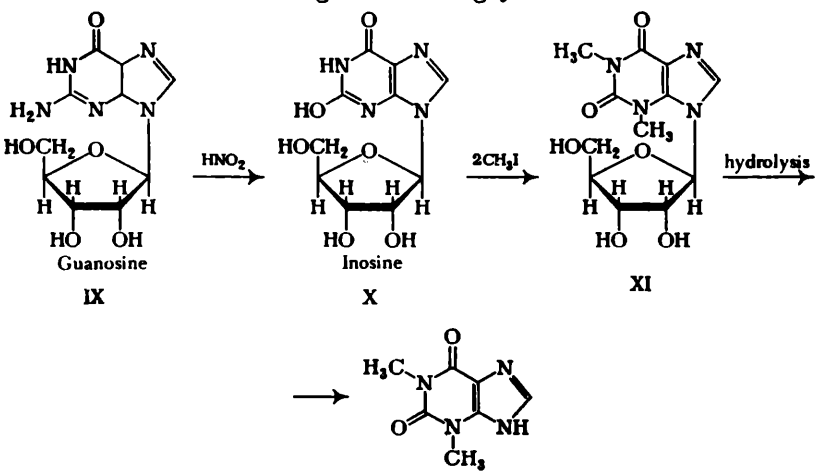
Cytidine Uridine VIII

VI VII

It is clear that the bond with the glycoside carbon atom was formed via the first nitrogen atom.

As regards the purine heterocycles, their linkage with the sugar cannot be formed through the amino group of guanine or adenine since the replacement of the amino group by a hydroxyl group by the action of nitrous acid takes place with the bond with the sugar being unaffected.

Purine nucleosides of the type of inosine X, obtained from guanosine IX by the action of nitrous acid, when reacted with methyl iodide are methylated at both nitrogen atoms of the six-membered ring, which rules out their linkage with the glycoside carbon.



Guanosine Inosine

IX X XI

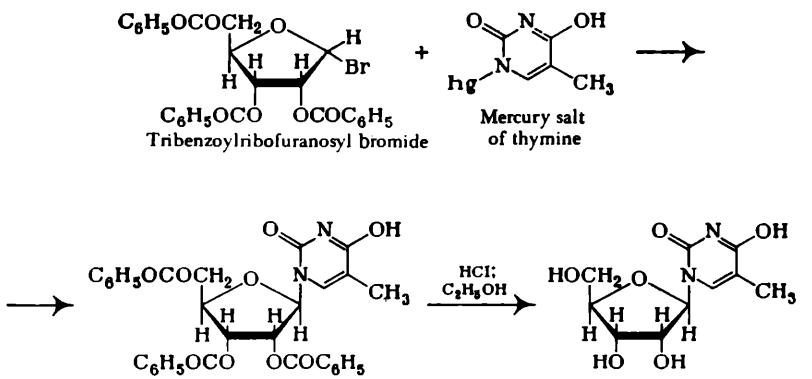
Theophylline

(Theophylline has already been considered in Volume III.)

The choice between the two nitrogen atoms of the five-membered ring has been made, in particular, on the basis of a comparison of the absorption spectra of adenosine, 9-methyladenine and 7-methyladenine; the spectra of the first two compounds have been found to be more closely related. This problem has also been solved by synthesis.

24.2. Synthesis of Nucleotides

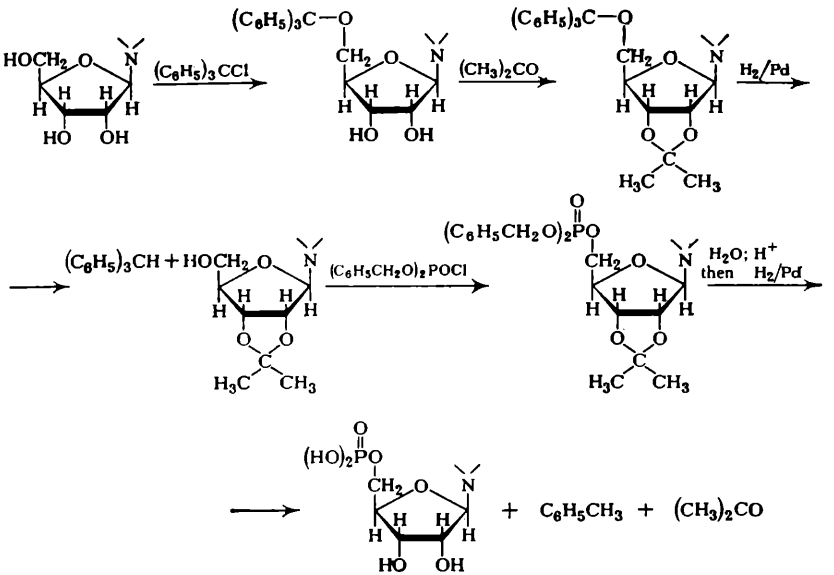
As an example of the synthesis of pyrimidine nucleosides, we shall cite the Fox synthesis of **ribothymidine** $\left(\text{hg} = \frac{1}{2}\,\text{Hg}\right)$:



Using dibenzoyldeoxyribofuranosyl bromide instead of tribenzoylribofuranosyl bromide, it is possible to obtain the corresponding deoxyribonucleosides.

The analogous route is applicable to the synthesis of purine nucleosides since the mercury atom displaces hydrogen exactly at the ninth nitrogen atom. If a purine has a free amino group, just as in guanine or adenine, it must be protected by benzoylation.

For nucleosides to be converted into nucleotides the primary alcoholic group of the sugar, for example, must be esterified with phosphoric acid. The other hydroxyl groups must be protected, which can be done in various ways, say, by the acetonation, in acid medium, of the two hydroxyls of ribose, which must be preliminarily tritylated at the primary alcoholic group:

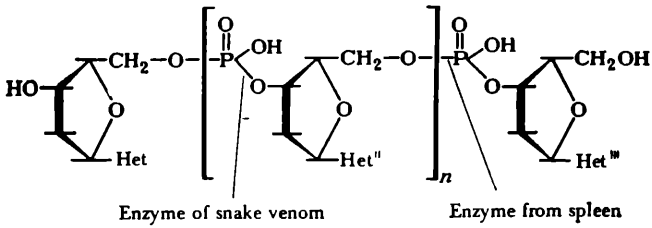


If the trityl derivative is phosphorylated with the secondary alcoholic groups being unprotected by acetonation, the phosphoric acid residue will esterify the hydroxyl group at the second or third carbon atom, and after the trityl group is removed by hydrogenolysis it is possible to obtain a nucleotide isomeric with the one shown above by the position of the phosphoric acid residue. The positions 5′ and 3′ are precisely the positions that are occupied by the phosphoric acid residue in natural nucleotides produced by the enzymatic hydrolysis of polynucleotides.

24.3. Polynucleotides

Polynucleotides, i.e., ribonucleic acids (RNA) and deoxyribonucleic acids (DNA), are macromolecular chains in which, according to analysis, there is one mole of sugar and one phosphoric acid residue per one mole of heterocycle. From the titration curve it follows that there is one hydroxyl group at each phosphorus atom, i.e., that polynucleotides are disubstituted esters of phosphoric acid which has retained one acid function. All facts allow us to establish the type of the primary structure of RNA and DNA. But the concrete primary structure of each individual RNA and DNA is determined, in addition, by the alternation of four heterocycles—two purine bases (adenine and guanine) and two pyrimidine bases (uracil and cytosine for RNA; thymine and cytosine for DNA). The method of establish-

ing this alternation, proposed by Khorana, consists in the selection of specific enzymes, one of which (from the spleen) splits the chain at the linkage between the phosphoric acid and the primary hydroxyl group (C-5′) and the other (from snake venom) does so at the linkage between the phosphoric acid and the secondary hydroxyl group (C-3′):



(Het=heterocycle residue)

Thus, it becomes possible to deduce the nature of the end groups and of the heterocycles Het′ and Het‴ linked to them.

In 1965, a team of American scientists headed by Robert W. Holley succeeded in establishing the total sequence of nucleotides in one of the lowest-molecular-weight soluble RNA—an alanine transfer RNA. The function of transfer RNA's is to bind amino acids and to carry them to ribosomes, where protein biosynthesis is effected by cross-linking of the amino acids in the sequence determined by the code of the DNA of the cell nucleus, which is transmitted to the ribosome by the messenger RNA. Each of the 20 amino acids has at least one corresponding transfer RNA. It will be informative if we consider briefly the work on the decoding of the alanine transfer RNA to such an extent as to give an idea of the method of complete elucidation of the sequence of nucleotides (bases) in a nucleic acid. We shall use the abbreviated designations employed by the authors of this remarkable work (see Table 24.1).

TABLE 24.1

A	Adenosine-3′-phosphate	p or —	Phosphoric acid residue
G	Guanosine-3′-phosphate	p!	2′,3′-Cyclic phosphate (e.g., Ip! = = inosine-2′,3′-cyclic phosphate)
I	Inosine-3′-phosphate		
C	Cytidine-3′-phosphate		
U	Uridine-3′-phosphate	Me	Methyl-
U*	A mixture of U and DiH-U	DiMe-	Dimethyl-
ψ	Pseudouridine-3′-phosphate	DiH-	Dihydro-
T	Ribothymidine-3′-phosphate	-OH	Free hydroxyl group
		DEAE-	Diethylaminoethyl-

As seen from this list of designations, even the lowest-molecular-weight type of RNA contains, along with the four "classical" heterocycles, their rarer, methylated or hydrogenated, derivatives that have not yet been mentioned in this book.

The sequence of nucleotides in the alanine transfer RNA which has been isolated from yeast and purified, was established by its hydrolysis with two different enzymes—the pancreatic ribonuclease and takadiastase TI ribonuclease. The hydrolysis by means of the two enzymes was carried out to completion. The total number of short nucleotides and mononucleotides obtained in each case was subjected to chromatographic separation; these polynucleotides (predominantly, di- and tri-, but not larger than octa-) were identified either by subsequent hydrolysis or by means of a comparison with known specimens with respect to R_f (see volume I, page 52). The results obtained were as follows.

The hydrolysis of the alanine transfer RNA by the pancreatic ribonuclease:

COH (terminal fragment)	G—G—G—A—G—A—G—U*—
13C—	Me-G—G—C—
ψ—	A—G—C—
6U—	A—G—DiH-U—
A—C—	G—A—U—
Me-I—ψ—	I—G—C—
DiMe-G—C—	G—G—T—
2G—C—	G—G—DiH-U—
3G—U—	G—G—A—C—
	pG—G—G—C—

The hydrolysis of the alanine tRNA by takadiastase TI ribonuclease:

9G	DiH-U—A—G—
pG—(initial fragment)	C—Me-I—ψ—G—
C—DiMe-Gp!	T—ψ—C—G—
U—Me-Gp!	A—C—U—C—G—
4C—G—	U—C—C—A—C—COH (terminal fragment)
2A—G—	U*—C—U—C—C—G—
U—G—	A—U—U—C—C—G—
U—A—G—	C—U—C—C—C—U—U—I—
DiH-U—C—G—	

A comparison of the two preceding schemes allows one to arrive at the conclusion that the alanine transfer RNA consists of the

following 16 fragments:

pG—G—G—C—	C—DiMe-C—
G—U—G—	C—U—C—C—C—U—U—I—G—C—
U—Me-G—G—C—	Me-I—ψ—
G—C—	G—G—G—A—G—A—G—U*—G—U—C—C—G—
G—U—A—G—	G—T—ψ—C—G—
DiH-U—C—G—	A—U—U—C—C—G—
G—DiH-U—A—G—	G—A—C—U—C—G—
C—G—	U—C—C—A—C—C—A-OH

The fragment that contains a free phosphoric acid residue (designated by p) is the left-hand end of the molecule, and the fragment with the free hydroxyl group is the right-hand end. The sequence of the remaining 14 fragments is not determined by these data. The agreement between the molecular weights determined experimentally and those calculated from the structure, including all the 16 units, confirms that there are no fragments missing.

Then follows the hydrolysis of the alanine transfer RNA again by TI ribonuclease but under mild conditions, which leads to much longer fragments (*a-k* on the scheme, see pages 438 and 439). Each of these fragments is hydrolysed, as described above for the parent RNA, by two enzymes, and the small fragments obtained allow us to establish the composition and sequence of the nucleotides in large fragments (from *a* to *k*). Since the principle is clear, the details are omitted here.

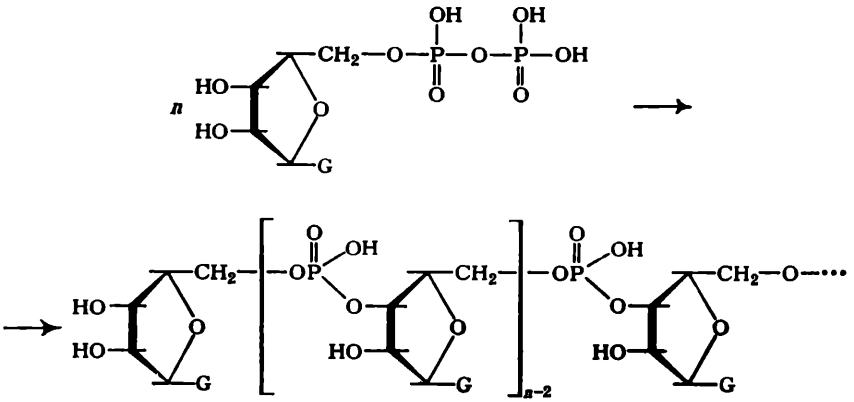
Having established the base composition and sequence in large fragments, we can arrange them in a definite sequence, taking advantage of the fact that they are partially superimposed by the sequence of nucleotides at their ends. For instance, the sequence of nucleotides in the middle of the fragment *i* (T—ψ—C—G—A—U—U—C—) proves that the fragment *f* with the right-hand end T—ψ—C—G— and the fragment *g* with the left-hand end A—U—U—C— are arranged directly (and without losses) one after the other. In this way it is possible to determine the complete sequence of the 77 nucleotides in the alanine transfer RNA molecule, which will be understood by the reader without any difficulty from the scheme given on pages 438 and 439.

At present, intensive research work is being carried out on the transfer RNAs for other amino acids; the structures of the tRNAs of serine, valine, tyrosine, and phenylalanine have already been determined. Of course, the difficulties that arise in the elucidation of the structure of RNA with a high molecular weight will be incomparably greater, though the principle may be the same.

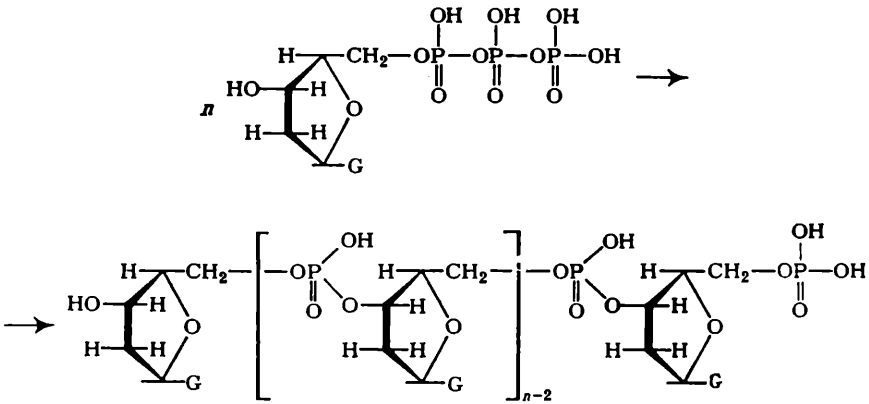
Of great importance is the enzymatic method of synthesis of polyribonucleotides from a nucleotide, discovered by Ochoa and

Grunberg-Manago and an analogous synthesis of polydeoxyribonucleotides from deoxynucleoside-5′-triphosphates effected by Kornberg.

The Ochoa-Grunberg-Manago synthesis is as follows (G is the guanine residue):



The Kornberg synthesis proceeds in the following way:



In the Ochoa method, the nucleotide is converted into a pyrophosphate which is then reacted with polynucleotide-phosphorylase, an enzyme isolated from one of the species of the bacterium *Azotobacter vinelandii*.

In this way there have been synthesized ribonucleic acids that do not occur in nature and have a regular structure built up of

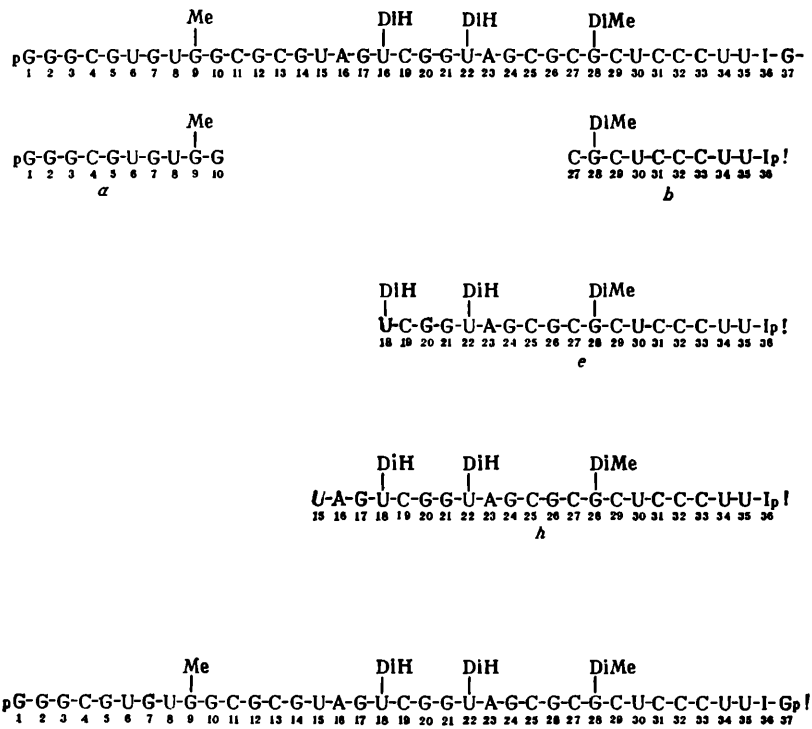
identical heterocyclic bases—polyadenylic, polyuridylic, polyinosinic acids, etc., which served as the simplest objects for the investigation of the secondary structure and properties of RNA's.

In the Kornberg method, use was made of the enzyme deoxynucleotidepolymerase (DNA polymerase) isolated by Kornberg from the bacterium *Escherichia coli*.

The fundamental difference between the Kornberg synthesis and the Ochoa-Grunberg-Manago synthesis consists (apart from the substrate and the enzyme) in the following.

1. The synthesis developed by Ochoa and Grunberg-Manago can be accomplished with an individual nucleoside pyrophosphate or with a mixture of such pyrophosphates. In the first case, a regularly built polyribonucleotide is produced, and in the second, a polynucleotide having the ribosophosphate skeleton of the same regularity, to which heterocyclic bases are linked in a random fashion.

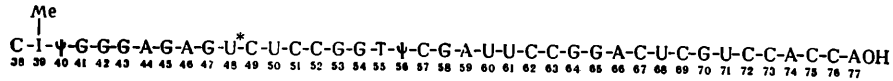
Alanine Transfer RNA Molecule

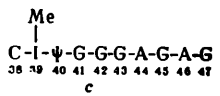


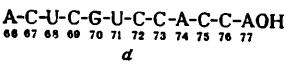
2. The Kornberg synthesis requires the use of a primer—a native DNA chain or its fragments and, as the pre-requisite, a mixture of the triphosphates of all the four nucleosides (adenosine, guanosine, thymidine, and cytosine). An amazing fact in this template synthesis is the replication of exactly the same DNA that was used as a primer, with the same base sequence as in the primer. The enzyme employed catalyses the synthesis of any DNA according to the template. The DNA primer operates even faster if it is heated in water up to 100°C, i.e., above the "melting" point at which hydrogen bonds, which are as important in DNA and RNA as in proteins, are cleaved.

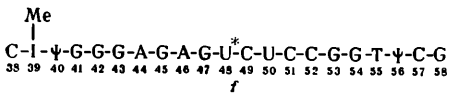
Now we shall discuss the problem of the secondary structure of DNA and RNA.

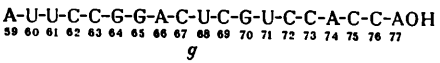
Just as Pauling worked out a model for proteins, so Crick and Watson developed a model of the polymer chain for DNA, proceed-

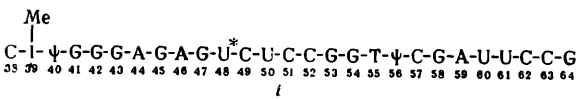


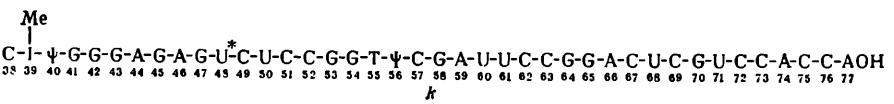












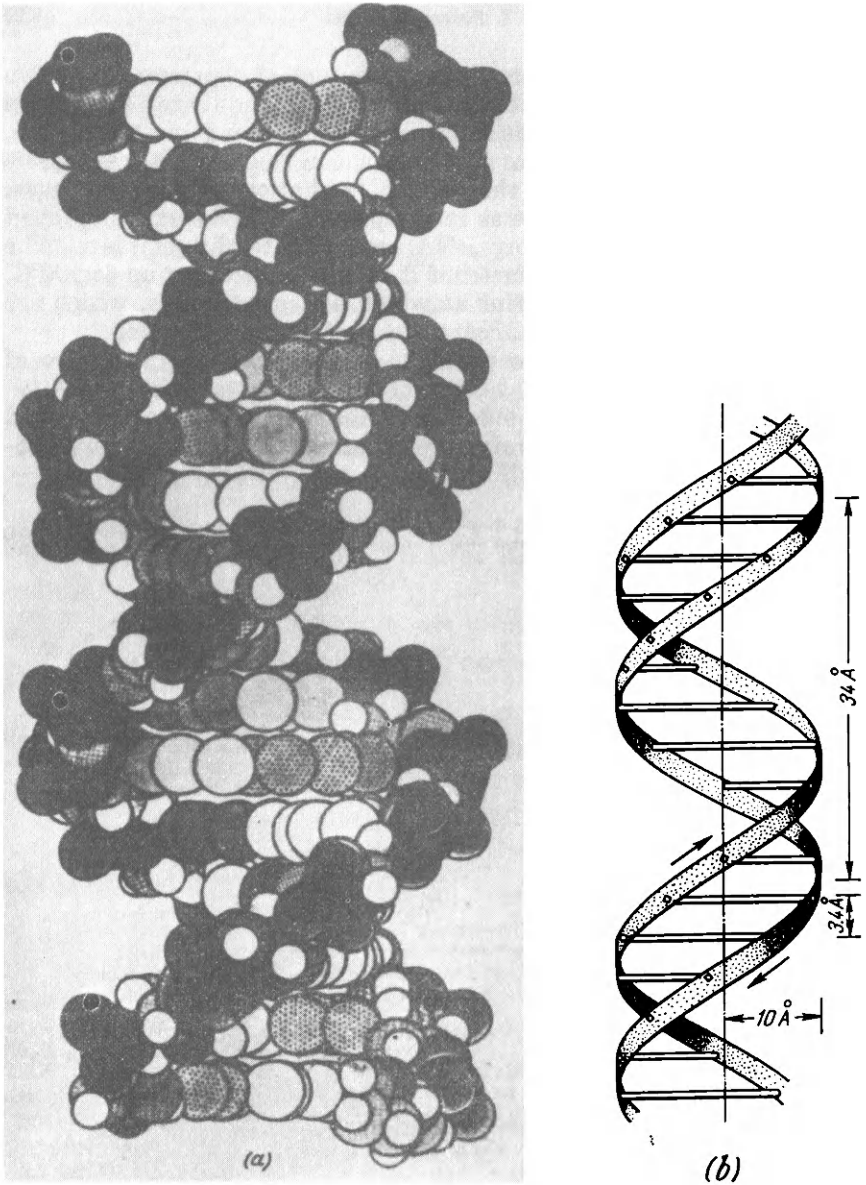
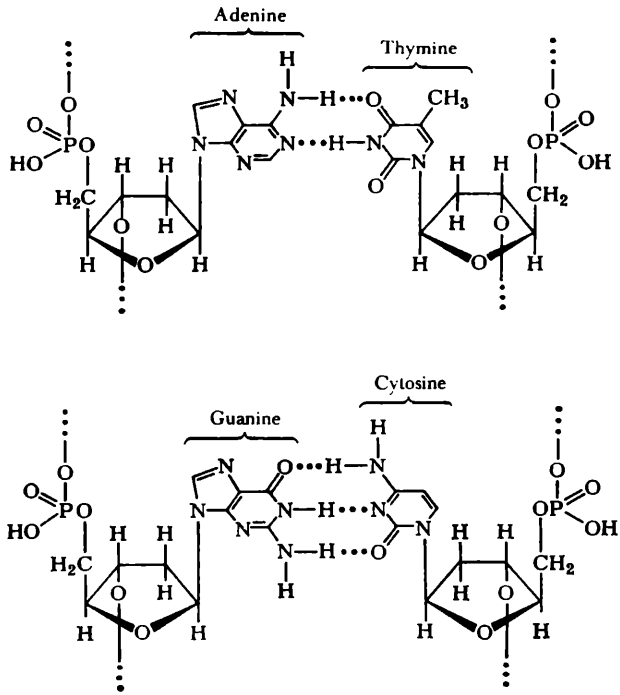


Fig. 24.1.

The model of a portion of the DNA molecule (*a*) and the DNA structure resembling a spiral ladder (*b*) in which the rungs represent the purine and pyrimidine bases linked by hydrogen bonds (F.H.C. Crick and J.D. Watson).

ing from the known interatomic distances and bond angles and the experimentally verified assumption of the determinative role of hydrogen bonds in the conformation of the molecule. In this case, the secondary structure of DNA consists of two deoxyribosophosphate chains intertwined with each other in the form of a double helix (Fig. 24.1). The DNA structure resembles a twisted spiral ladder in which the side pieces (two strands of nucleic acids—alternating units of deoxyribose and phosphate) are oriented toward each other. The rungs are formed by the bases paired in a special way and held together by hydrogen bonds. The purine and pyrimidine bases are always paired in such a way that guanine is bonded to cytosine and adenine to thymine. Thus, the rungs of the spiral ladder of the DNA molecule will invariably be of the following two types:



Crick and Watson (1953) succeeded in verifying the principal conclusions of their hypothesis with the aid of the X-ray diffraction pattern of the stretched strand of the DNA molecule. Since then their hypothesis has received numerous confirmations. From this it is clear that in the DNA chain the number of guanine molecules must be equal to the number of cytosine molecules, and the same principle is valid for the other complementary pair, adenine and

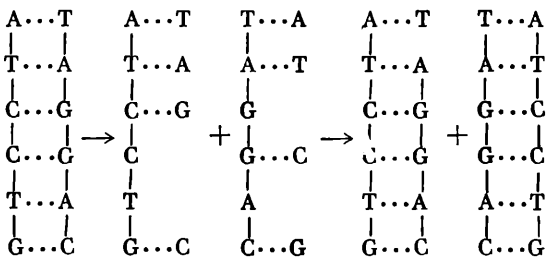
thymine. Such is the simple explanation for Chargaff's pairing rule established empirically on the basis of the analysis of various deoxyribonucleic acids. This rule states that the molar ratios of the nitrogen-containing bases (adenine/thymine and guanine/cytosine) in DNA molecules are always close to unity. The same holds true for the adenine/uracil and guanine/cytosine ratios in ribonucleic acids (RNA).

The Kornberg synthesis with a primer or, as commonly said, with a template, is simply explained on the basis of this model. Let us designate portions of the macromolecule with adenine, guanine, thymine, and cytosine by the letters A, G, T, and C, respectively, and the hydrogen bond by three dots. Then the above formulas will assume the following form:

A···T
G···C

The mononucleosides linked to the phosphoric acid, which were not included in the macromolecules, will be denoted by the same letters. Then the spiral ladder of the DNA primer (template) will be represented by a certain definite sequence of the letters connected through the dots of hydrogen bonds with the corresponding letters that represent the parts of additional nucleotides.

Suppose that the hydrogen bonds are broken (all at once or gradually, along the entire ladder or a part of it), say, on heating the DNA primer in water, which, as has been said, speeds up the process of synthesis. Then each of the two strands will take up from the medium and select nucleosides that are capable of forming hydrogen bonds with the corresponding units, and the enzyme will cross-link them by phosphate bonds if the nucleosides will fit in size. Otherwise, they will sooner or later be broken and replaced by a new nucleoside and so on until the last one is "sewn in". Thus, *reduplication* (doubling) will inevitably take place if there are enough nucleotides (in the form of their triphosphates) in the medium, the two "ladders" being an exact replica of the template:



(chains broke apart, and each takes complementary nucleotides from medium)

In Kornberg experiments the amount of deoxyribonucleic acid (primer) was increased by 20 times.

The same process, according to the modern conceptions, forms the basis of cell division by way of the long known process called **mitosis** in biology. This process consists in the following. Rod-shaped chromosomes (visible under the microscope) composed of deoxyribonucleic acids are formed inside the cell nucleus. Each chromosome is split into two halves in a longitudinal direction; these sister chromosomes separate to the opposite ends of the cell and each is supplemented to a full chromosome. Then the cell is divided by a wall into two sister cells and the chromosomes present in each new cell again form a nucleus. It is not difficult to see that the process of reduplication of chromosomes is based on the reduplication of DNA strands just described. Taking into account that each living organism arises from a single cell, it is obvious that each cell of a multicellular organism has the full complement of chromosomes and, hence, a complete set of the deoxyribonucleic acids of the parental cell as a result of the mitotic cell division. If the parental cell originates from the fusion of the mother and father cells (each of them having only one set of chromosomes, that is, only one member of each chromosome pair) then, as a result, each cell of the organism receives half the number of chromosomes (and DNA) of the father type and half of those of the mother type.

The process of reduplication of DNA taking place during mitosis has been confirmed by the use of labelled atoms. We shall cite only an experiment with labelled nitrogen. A bacterial culture was grown in a medium containing only ^{15}N and was then transferred to a medium with ^{14}N, where it continued to grow. Samples of the biomass were removed at various time intervals, deoxyribonucleic acids were extracted from them and its macromolecules were subjected to centrifugation in a solution of cesium chloride having a density intermediate between the densities of the DNA strands from cells grown entirely on ^{14}N and ^{15}N culture mediums. The DNA fractions separated by this method were found to have no macromolecules with randomly mixed ^{14}N and ^{15}N atoms. There were three distinct groups: DNA completely built up of ^{15}N; DNA containing only ^{14}N; and DNA with 50 per cent of ^{14}N and 50 per cent of ^{15}N. Thus, one chain of the double helix of DNA is virtually completely transferred to the next generation, and the second half of the helix is complemented by the available nucleoside phosphate material.

Another experiment that illustrates the role of DNA consists in the following. As has already been said, bacteriophages (bacterium eaters; for short, they are often referred to as phages) are bacterial viruses. It is possible to observe under the electron microscope how such a tiny organism-like particle attacks a bacterium (a large cell) and attaches itself to its prey by the tip of its tail. It then makes

a hole in the bacterial wall (more exactly, it dissolves part of the wall with the aid of the enzyme liberated) and, using its tail rather like an injection needle, injects the contents of the head (deoxyribonucleic acid) into the bacterium. The protein head easily separates from the bacterium and does not take part in the subsequent events. There has been grown a bacteriophage (of the T_2 type) labelled by radioactive phosphorus in the nucleic acid and by radioactive sulphur in the protein (Hershey and Chase). As a result of a radiochemical analysis, it has been found that only the radioactive phosphorus (i.e., DNA) gets into the bacterium, the radioactive sulphur being left in the phage head. Then the viruses multiply inside the bacterium and finally cause them to burst (bacterial lysis), liberating many new virus particles. Thus, it is clear, and this has been confirmed by numerous other arguments and experiments, that DNA is responsible for its own multiplication (repeated reduplication) and the synthesis of protein in accordance with the "code" contained in the DNA structure. In other words, DNA is a carrier of information on the future structure of proteins synthesized with its participation.

Digressing from viruses and phages and returning to cells, let us recall that, as known from cytology, the DNA of the cell is concentrated in the nucleus (in chromosomes) and that protein synthesis takes place in particles called **ribosomes** which are in the cytoplasm, outside the nucleus, and which contain only a high-molecular-weight ribonucleic acid. The investigation of this problem has led to the conclusion that the functions of the chromosomal DNA and of the ribosomal RNA are quite different: DNA only stores information and ribosomes serve as the site for the synthesis of proteins, whose structure is dictated by DNA. But how is this information delivered from the DNA to the ribosomes?

At present there is conclusive evidence for the existence in the cell of relatively low-molecular-weight messenger ribonucleic acids synthesized on DNA which acts as a template, i.e., so that to the template A, G, T, and C there correspond U (uracil in place of thymine since this is RNA) C, A, and G. These messenger-RNA's, carrying a transcript of the DNA genetic code, pass to the ribosomes, where they are fixed on the ribosomal RNA (rRNA), and transmit the information on the type of proteins that are to be synthesized by the ribosomes. In principle, the accumulation of protein molecules takes place exactly on mRNA's, which are therefore also called template RNA's (the information code will be discussed at a later time). This has been proved, in particular, in the following way (Volkin, Astrachan): bacteria were infected with a phage, and then the radioactive phosphate labelled with ^{32}P was introduced into the medium. After the lapse of 1-3 min the bacteria lysed. Then all the RNA was separated and the total amount of each heterocyclic base

(A, G, C, U) was determined in it, and separately, the ratio of the nucleotides labelled at the phosphorus to the same bases. Whereas the DNA composition of the phage did not match the RNA composition on the whole, it was found that the phage DNA composition matched the amount of radioactive nucleotides from RNA as was expected, i.e., the following relation was obtained:

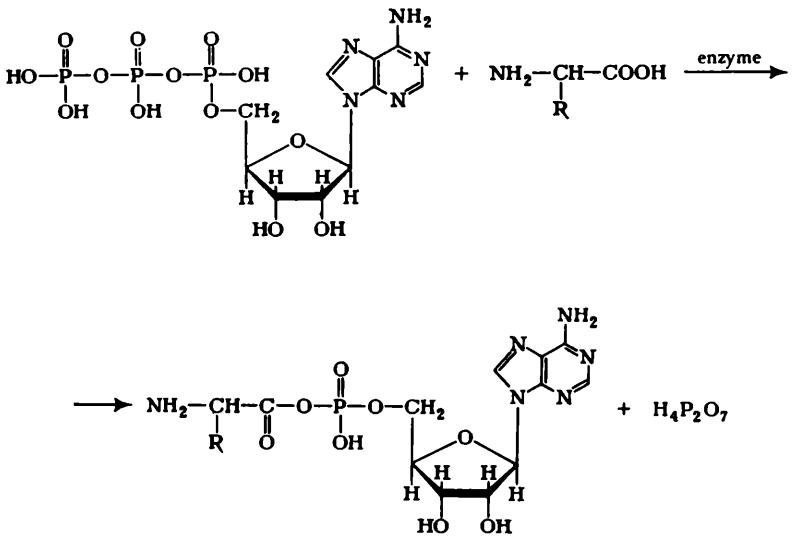
$$\underset{\text{(In DNA)}}{\frac{A+T}{C+G}} = \underset{\text{(in RNA)}}{\frac{{}^*A+{}^*U}{{}^*C+{}^*G}}$$

(nucleotides labelled with ^{32}P are marked with asterisk)

Hence, during the short period of time between the introduction of ^{32}P into the medium and the destruction of the bacteria there were synthesized only messenger RNA's, and not ribosomal RNA's, and only the mRNA received ^{32}P. It should also be noted that there was 1 per cent of mRNA in the total amount of RNA in the cell and 90 per cent of ribosomal RNA, the remainder being low-molecular-weight soluble ribonucleic acids, the role of which will be clarified below. Therefore, a change in the mRNA composition (only 1 per cent) does not affect the total RNA composition. After the cells (e.g., bacteria) were destroyed, the ribosomes were separated on the centrifuge, introduced into the required enzymatic medium and thus made to produce the protein. Instead of mRNA, a foreign RNA was introduced, e.g., of bacteriophage *f*-2 (this phage contains only RNA and protein). This foreign RNA acted in this case as mRNA and the bacterial ribosomes produced a foreign protein—the protein of the phage shell (M. W. Nirenberg, H. Fraenkel-Conrat *et al*). No less surprising is Nirenberg's experiment. To a suspension of ribosomes in a solution of enzymes, in which there is a complete set of all the 20 amino acids, there was added a synthetic polynucleotide as mRNA, say, polyuridine phosphate. In this case the ribosomes produced a protein of regular structure, namely polyphenylalanine. Note this fact which is fundamental for the deciphering of the DNA code (page 447).

What is the role of the third group of RNA which constitutes up to 10 per cent of the total amount of RNA in the cell and which are neither high-molecular-weight ribosomal RNA nor messenger RNA. This is the so-called transfer RNA which is a relatively low molar mass nucleic acid (its molecular mass is of the order of 25,000). Its function is to isolate the free amino acids from the medium and to carry these amino acids, supplied with the genetic code of tRNA, to the ribosomes. Evidently, the meaning of this consists, in particular, in protecting the amino acids from other kinds of metabolism, say, from oxidation and energetic combustion, which requires a lesser or greater amount of amino acids—the products of protein food digestion. The main function, however, is to supply the amino acid with a code. The first reaction in which the amino acid is bound is

the interaction of its carboxyl group with adenosine triphosphate with the formation of a phosphate bond (each of the 20 amino acids requires a specific enzyme):



Then the amino acid residue passes into the molecule of a soluble tRNA specific to a given amino acid, the amino acid acylating one of the two secondary hydroxyl groups of the ribose of the tRNA terminal nucleoside. This is seen from the fact that, in contrast to a free tRNA, the transfer RNA that has bound the amino-acid molecule, is not oxidized by periodic acid, like all *cis*-glycols (see Volume II, page 125), i.e., one of its two hydroxyl groups is acylated. The manner in which the ribosomal, messenger and transfer RNA's interact with the combined amino acid is clarified by Lipmann's experiments in which the position of the amino acid in the polypeptide chain is determined only by the interaction between the codon* (on mRNA) and the anticodon (on tRNA).

This is proved directly as follows.

The cysteine tRNA was preliminarily loaded with cysteine labelled with ^{14}C. Then cysteine was mildly reduced (over Raney nickel) to

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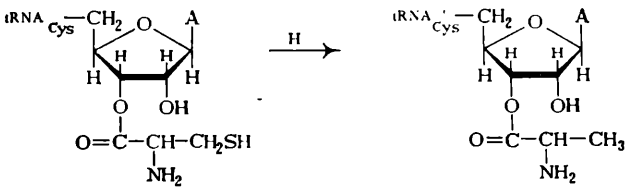
* The *codon* in this case is a region of messenger RNA, consisting of three nucleotides which code the amino acid to be incorporated into the protein. The *anticodon* consists of the other three complementary nucleotides which are in this case contained in tRNA:

alanine:



Thus, the cysteine tRNA was found to be linked to alanine.

Then, this tRNA combined with alanine was placed in a system which synthesizes hemoglobin (the system contained mRNA specific to hemoglobin). The analysis of the resulting polypeptide chains of hemoglobin showed that the cysteine in them had been replaced by alanine. Hence, the ribosomal RNA did not participate in the determination of the amino-acid sequence.

Determination of the Nucleotide Sequence in the Codon. Recall that the amino-acid sequence in the protein synthesized in the ribosome is dictated by the chromosomal DNA. This DNA-coded order is conveyed to the ribosome by means of the transfer RNA, which is a firmly established fact. It is evident that the DNA code contains information for the base sequence in the chromosome, more exactly, on a part of it, which gives a replica to mRNA. Since there are 4 species of bases and 20 amino acids in DNA, it follows that one base cannot specify a particular amino acid. Two bases are not enough either since $4^2 = 16$. But three bases ($4^3 = 64$) are more than enough. Thus, it is evidently the number 3, not a larger one. Recall that in Nirenberg's experiments polyuridine phosphate was used as mRNA. In this case, the ribosomes synthesized polyphenylalanine as the only protein. From this we may conclude that the phenylalanine codon is U—U—U (three uridinephosphate units in the mRNA molecule). Using synthetic polynucleotides with a regular structure (one base) and with a random structure, but with different ratios of the bases and applying theory of probability, it has proved possible to establish the base triplets in the codon for all the 20 amino acids. The base sequence in the codon has been elucidated by the work of Nirenberg and his collaborators, published in 1965. In many cases, the code was found to be *degenerate*. This means that the same amino acid is specified not by one triplet code but by two or more triplet codes.

As has been established by Nirenberg and his collaborators (1965), the tRNA's that carry amino acids become attached to the ribosomes only if there is a corresponding mRNA on the ribosomes. If the role of mRNA is played by a synthetic polyribonucleotide (say, polyuridine phosphate), the tRNA that becomes linked to the ribosomes must

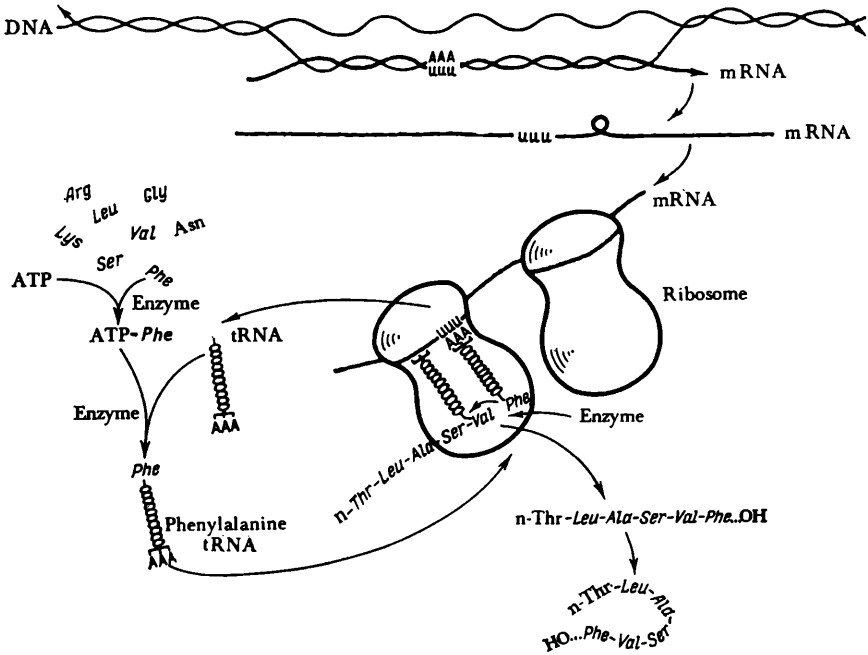


Fig. 24.2.

The synthesis of proteins in the living cell:

DNA—deoxyribonucleic acid; mRNA—messenger ribonucleic acid which takes the genetic instructions UUU from the AAA codon of DNA; ATP—adenosine triphosphate which activates the amino acids and binds them with RNA (tRNA); one of the ribosomes on the left has received mRNA and selects tRNA (charged with amino acids) according to their codons, in this case, AAA.

contain a corresponding anticodon in its structure. Thus, for UUU this is A—A—A which is present only in the phenylalanine tRNA. The scheme of the total protein synthesis in the cell is given in Fig. 24.2. It has been found that in these experiments (the binding of tRNA with ribosomes), the polyribonucleotide may be replaced by a trinucleotide and the base sequence in the codon can thus be precisely determined. For example, the linking of the leucine tRNA to the ribosomes and the incorporation of leucine in the protein is specified by the codon UUG, and if the same three bases are arranged as GUU or UGU in the trinucleotide which plays the role of mRNA, then the leucine tRNA does not become attached to the ribosomes.

In this way the sequence of nucleotides (any of the triplets) in the codons for all the amino acids have been determined (Table 24.2).

The messenger RNA conveys to the ribosome a continuous chain of codons bound in the molecule of this mRNA. The transfer RNA carries to the ribosome the amino acids supplied with anticodons

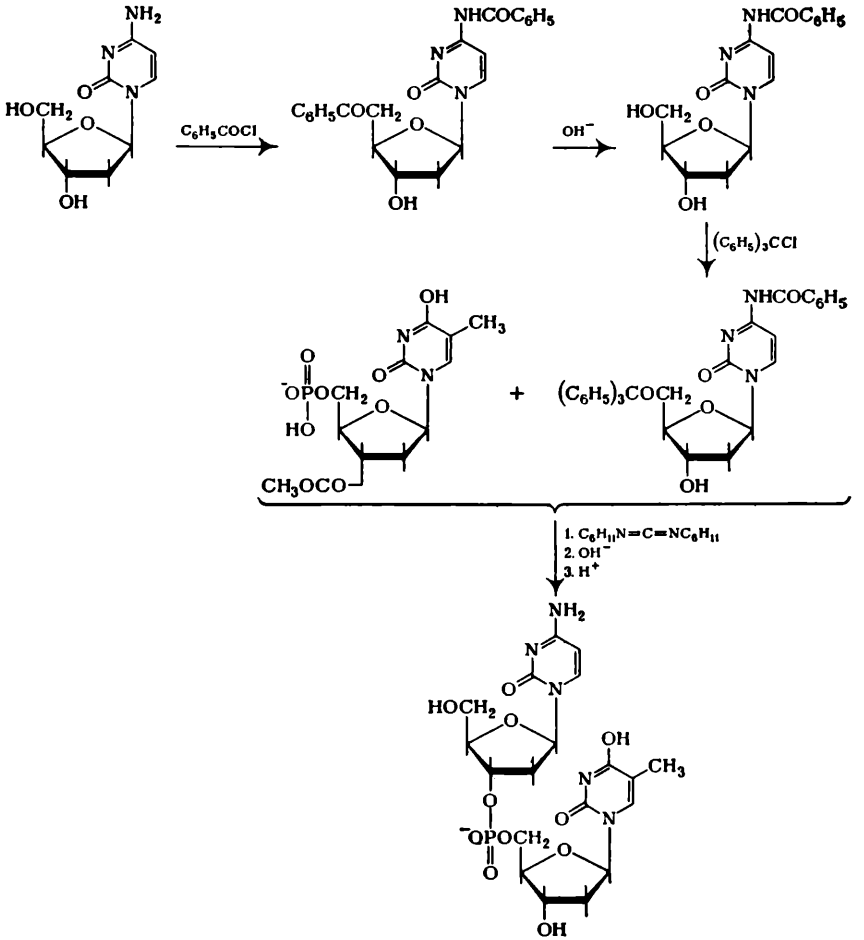
TABLE 24.2. The Genetic Code of RNA

First codon nucleotide	Second codon nucleotide: U	Second codon nucleotide: C	Second codon nucleotide: A	Second codon nucleotide: G	Third codon nucleotide
U	UUU, UUC: Phenylalanine (Phe)	UCU, UCC, UCA, UCG: Seryl (Ser)	UAU, UAC: Tyrosyl (Tyr)	UGU, UGC: Cysteinyl (Cys)	U C A G
	UUA, UUG: Leucyl (Leu)		UAA, UAG	UGA; UGG: Tryptophanyl (Try)	
C	CUU, CUC, CUA, CUG: Leucyl (Leu)	CCU, CCC, CCA, CCG: Prolyl (Pro)	CAU, CAC: Histidyl (His); CAA, CAG: Glutaminyl (Glu N)	CGU, CGC, CGA, CGG: Arginyl (Arg)	U C A G
A	AUU, AUC, AUA: Isoleucyl (Ileu)	ACU, ACC, ACA, ACG: Threonyl (Thr)	AAU, AAC: Asparaginyl (Asp N); AAA, AAG: Lysyl (Lys)	AGU, AGC: Seryl (Ser); AGA, AGG: Arginyl (Arg)	U C A G
	AUG: Methionyl (Met)				
G	GUU, GUC, GUA, GUG: Valyl (Val)	GCU, GCC, GCA, GCG: Alanyl (Ala)	GAU, GAC: Aspartyl (Asp); GAA, GAG: Glytamyl (Glu)	GGU, GGC, GGA, GGG: Glycyl (Gly)	U C A G

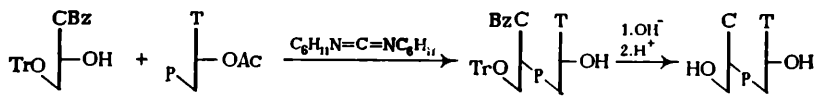
(complementary to the codon), which allow the amino acids to be fixed on the mRNA and to begin collecting the protein molecule. It is necessary, however, to disclose another essential detail of this collecting process: the punctuation marks in this continuous chain of bases. Evidently, the result of reading the chain of triplet codes will be different, depending on the point from which the reading of this continuous line is started. It has been found that probably it is always the methionine code AUG, and the methionine molecule (namely, formylmethionine) is incorporated into the start point of the protein chain, although it may have to be split off later. Further reading of the code is specified in the form of subsequent triplets. And how long is this to be continued? It turns out that this is to be done until there appears one of the nonsense codons, i.e., codons that apparently do not code for any amino acid, namely, UAG or UAA (the first is conventionally called the ochre and the second, the amber).

It is interesting that the action of a number of antibiotics boils down to creating obstacles to any of the stages of this process. Tetracycline antibiotics (Volume III, page 306) prevent the tRNA carrying an amino acid from being attached to the complementary codon of mRNA in the ribosome. Streptomycin and actinomycin interfere with the replication of DNA and RNA. Puromycin itself takes the place of the end portion on tRNA, interrupting thereby the protein synthesis. Chloriomycetin retards the last stage of protein synthesis — the binding of amino acids into the polypeptide chain.

Synthesis of DNA and RNA. Before discussing the synthesis of DNA and RNA it is appropriate to consider the binding of a nucleoside and a nucleotide into a dinucleotide. The difficulty lies in joining two nucleotides together by the phosphate bridge. For this purpose, the hydroxyl groups that are not to be involved in the bond must be protected and, besides, the amino group (for example, of the pyrimidine ring) must also be protected. The secondary hydroxyl groups are protected by benzoylation or acetylation, the primary hydroxyls by tritylation [by the action of $(C_6H_5)_3CCl$], and the amino groups by benzoylation. The union via the phosphate bridge is accomplished by the action of a diacid phosphoric ester of a nucleoside (i.e., a nucleotide) on a second nucleotide protected as described above in the presence of a dehydrating agent, dicyclohexylcarbodiimide. The scheme of the synthesis of a **dinucleotide** containing cytosine and thymine as the pyrimidine bases is as follows:



This synthesis may also be represented by the following simplified scheme:

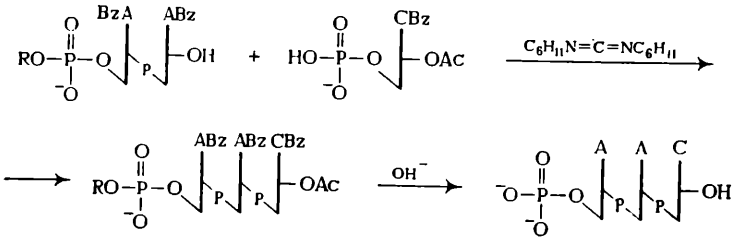


Here (and afterwards) the following abbreviations are used:

C = cytosine	Tr = trityl (triphenylmethyl)
T = thymine	p = phosphoric acid residue
G = guanine	Bz = benzoyl
A = adenine	Ac = acetyl

The scheme shows only the primary hydroxyl group (the fifth), the secondary hydroxyl (the third) and the heterocyclic base. The other groupings are omitted since they do not take part in the synthesis.

The synthesis of a **trinucleotide** can be represented by in an analogous way.



Using this principle, Khorana synthesized tetranucleotides. Two protected tetranucleotides were used to produce an octanucleotide, which together with a tetranucleotide served as the starting point for the synthesis of a dodecanucleotide and, finally, the dodecanucleotide and tetranucleotide were employed for producing a hexadecanucleotide. Other oligonucleotides have also been obtained.

From the schemes given it becomes clear that the sequence of the heterocyclic bases in such a synthetic polynucleotide depends on their sequence in all the fragmentary polynucleotides taken for the synthesis, i.e., on the wish of the synthesizing chemist. Such a multistage synthesis, however, is not only tedious, but the yield of the polynucleotide is extremely low, and the polynucleotide chain containing several tens of nucleotide units cannot in general be built in this way.

The route of the synthesis of longer DNA chains is based on the use of enzymes for the cross-linking, via phosphate bonds, of relatively short polynucleotide chains (*oligonucleotides*) fixed on the template to form long chains. The action of enzymes in this case may be illustrated by the following examples.

Figure 24.3 shows a double helix of DNA which is partially separated by the enzyme exonuclease, and the separated ends when acted on by the enzyme polymerase are built up due to the complementary nucleotides from the medium, which are cross-linked into a chain (the dashed portions of the first right-handed helix) (Kornberg). In recent years there has also been discovered an enzyme, ligase, which cross-links, through phosphate bridges, two neighbouring oligonucleotides fixed on a template (Fig. 24.4). The energy consumed is supplied by adenosine triphosphate (ATP). On the left side of Fig. 24.4 is shown a portion of the double helix of DNA, the chains of which are joined together by the hydrogen bonds of the

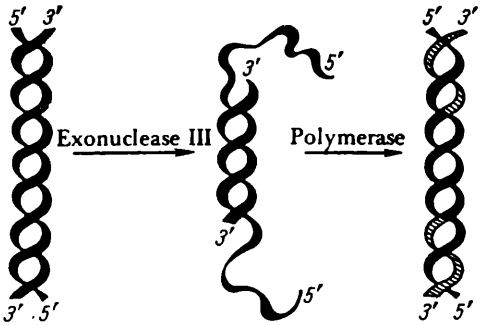


Fig. 24.3.

complementary heterocyclic bases, A···T and G···C. The lower chain is broken in the middle, one of the oligonucleotides having a phosphate group at its end and the other, a hydroxyl group. The two oligonucleotides are found to be cross-linked by the action of the enzyme and ATP. The principle of complementing the DNA template

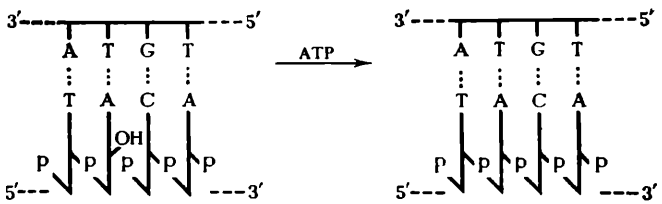


Fig. 24.4.

with nucleotides and of the enzymatic cross-linking of the nucleotides on the template by means of phosphate bridges has enabled (Khorana) building up a chain complementary to the parent DNA, which may even be synthetic. The scheme on page 456 illustrates the use of the Khorana method for synthesis of portions of a real DNA and cross-linking of the portions obtained into a complete DNA molecule of desired structure.

The line *a* represents the sequence of nucleotides from 1 to 30 in the alanine transfer RNA, and the line *a′* is the sequence of nucleotides 21-50 of the same RNA.

The line *b* represents a single-strand fragment of DNA obtained by synthesis, which consists of units that are complementary to the units 1-20 of the parent tRNA; the line *b′* is a single-strand fragment of a synthetic DNA, which consists of nucleotides complementary to the units 21-40 of the line *a′*. The bottom lines *c* and *c′* also represent the fragments of a synthetic DNA, but here only the right-

hand ends consisting of 10 units are complementary to the 10 nucleotides of DNA represented by the lines *b* and *b'* and are linked to them, and the left-hand ends (also consisting of 10 units) are free.

In the presence of a mixture of the corresponding mononucleotides, the free ends of synthetic DNA's in the lines *b*, *b'*, *c* and *c'* can be supplemented by the complementary nucleotides, which are then joined together into a chain by the action of polymerase. The role of the 10 intermediate nucleotides of the lines *b*, *c*, *b'*, and *c'* is to link the chains of the synthetic polynucleotide. Thus, as a result, two

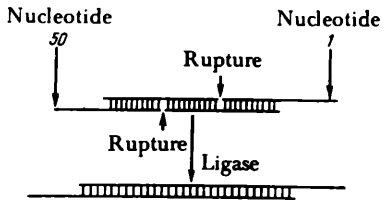


Fig. 24.5.

portions of the DNA codons of a transfer ribonucleic acid are produced from synthetic oligonucleotides consisting each of 20 nucleotides. The first portion is composed of 30 nucleotides (from 1 to 30), the second, also 30 (from 21 to 50); the nucleotides from 21 to 30 in the lines *c* and *b'* are complementary. After they are complemented to form full double strands and these strands are separated, the built-up (not shown in Fig. 24.4) strands *c* and *b'* can be joined together by means of these ten complementary nucleotides (21-30). This must be followed by a new complementing of the free ends, i.e., 1-20 and 31-50. Thus, the template synthesis of a polynucleotide with the sequence of units complementary to the units of alanine tRNA from 1 to 50 will be completed.

A modification of the above route of synthesis of a portion of the DNA chain, complementary to the chain of the first 50 nucleotides of alanine tRNA is illustrated in Fig. 24.5. The four chains of nucleotides shown by the horizontal lines at the top of Fig. 24.5 are to be synthesized. Each of these four chains contains 20 nucleotides. The chains are built up in such a manner that the upper right-hand line corresponds to the 20 nucleotides of DNA, which are complementary to the right-hand 20 nucleotides of alanine tRNA, and the upper left-hand line corresponds to the next 20 nucleotides. The two bottom horizontal lines also represent two DNA portions consisting each of 20 nucleotides, of which 20 + 10 nucleotides are complementary to the corresponding 30 nucleotides of the two upper chains. On the whole, there is obtained a system of four DNA chains rigidly

linked by 30 pairs of complementary nucleotides. This system has free ends with 10 nucleotides in the upper and the lower chain. There are two ruptured points in the phosphate bonds, which are marked with arrows. These ruptured points are "sewed up" by the action of the enzyme ligase, and phosphate bridges appear at these sites. Thus, the four starting polynucleotides are converted into two chains, which are joined together in the middle part in a complementary way. What remains is to build up the two free ends of the

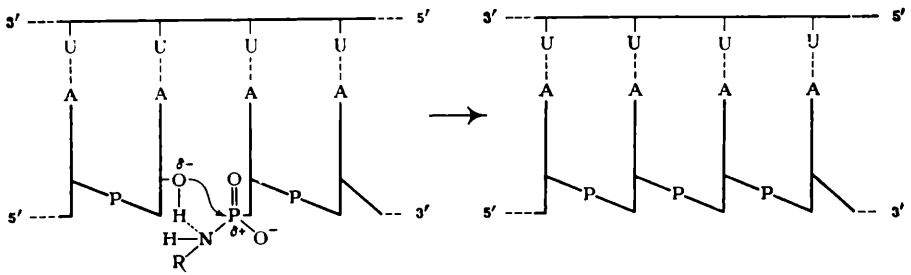


Fig. 24.6.

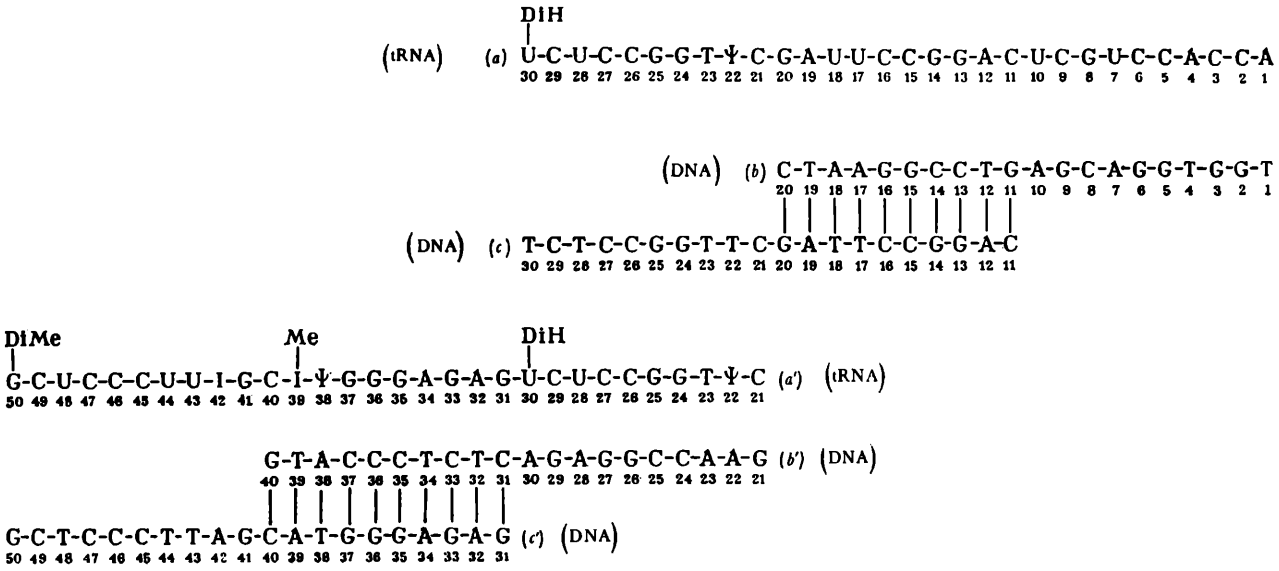
molecule with the aid of polymerase and a set of free nucleotides in a complementary manner, and the desired double helix consisting of 50 polynucleotides will be complete. One of its chains is complementary to the first 50 nucleotides of tRNA, and the other is complementary to the first.

Using either of these two synthesis pathways, it is possible to build a DNA from 77 polynucleotides complementary to the entire alanine tRNA molecule and to accomplish the template synthesis of the tRNA itself on it. Khorana carried out this synthesis in 1968.

A chemical method was proposed in 1970 (M. A. Prokofiev and Z. A. Shabarova) for closing the ruptured points in complementary polynucleotides, instead of the enzymatic route (the use of ligase). The phosphate group at the site of ruptured phosphate bonds is synthetically converted into the amido-phosphate bond. When it approaches the end hydroxyl group of the neighbouring block and is at a distance of a covalent bond (which must be provided by the complementary properties of the two chains), the groups at the ruptured site are mutually activated due to the formation of a hydrogen bond: the hydroxyl group assumes the properties of the alkoxy ion, and the phosphorus atom becomes more electrophilic (Fig. 24.6; R = amino-acid residue).

The nucleophilic attack on the phosphorus atom results in the formation of a covalent phosphodiester bond (a phosphate bridge). Without a complementary polynucleotide the end amido-phosphate and hydroxyl groups of oligonucleotides do not interact since they

Synthesis of DNA Fragment of Specified Structure



cannot approach each other because of the complexity of the spatial structure of the reacting oligonucleotides. The proposed reaction, which resembles the enzymatic process in certain respects (the directed approach of the reacting groups in space, which results in their mutual activation) will make it possible to accomplish a complete chemical synthesis of the genetic material under conditions very similar to natural conditions.

The amino-acid code and the entire mechanism of protein synthesis are the same for all living organisms—from the bacterium to the human being. The chromosomes of the first cell that starts building the organism already contains, in the form of DNA, all the information on the proteins to be synthesized by the organism and, what is especially important, on the protein enzymes which are to be synthesized by the organism and which will determine the entire biochemical development of its life. In the bacterial cell, according to crude estimates, there operate more than 1000 different enzymes and this is the basis of its vital activity. The structure of each of them is dictated by a certain portion of the DNA strand, called the **cistron** which is the gene localized on the chromosome strand in the form of a certain sequence of nucleotides. The chromosomes with their cistrons are transferred during the mitotic division to each cell of the organism. When the sex cells are being formed, they are supplied by one set of chromosomes that is, one member of each chromosome pair (haploid cells); the other set comes from the fusion of the father and mother cells, and thus the fertilized cell—the parent cell of the future organism—receives the genetic information from both parents.

Experimental evidence has recently been obtained, according to which the nucleic acids may be considered to be responsible for the chemistry of memory—from the simplest worms to higher animals.

In 1970 Khorana accomplished the synthesis of a gene consisting of 10-unit fragments, using the second route (with the aid of ligase). Replications (tRNA) have not yet been obtained.

Chapter 25

Enzymes

The numerous biochemical reactions that take place in plant and animal organisms and in their cells and also in unicellular microorganisms are made possible only through the action of biological catalysts called **enzymes** (from the Greek "in yeast").

Enzymes may be simple or conjugated proteins, that is, proteins united with the non-protein prosthetic group. The number of known enzymes is very great. It is believed that a single bacterial cell uses up to 1000 various enzymes. Structures, however, have been established for only a few enzymes. Examples of purely protein enzymes are proteolytic enzymes of the digestive tract, such as pepsin and trypsin. Cases are known where the same protein performs both the structural and enzymatic functions in the organism. As examples may be cited the muscle protein myosin, which catalytically decomposes adenosine triphosphate, a reaction which in this particular case provides the muscle contraction energy (V. A. Engelhardt, M. N. Lyubimova).

An important group of oxidation-reduction (redox) enzymes contain, as a rule, prosthetic groups, including nitrogenous heterocycles, which perform redox functions. In cases where the non-protein component of the enzyme is responsible for the specific enzymatic activity, the prosthetic group is called the **coenzyme**, and the protein portion, the **apoenzyme.** The coenzyme determines the reaction specificity—the direction of the reaction or, in other words, the reaction out of the numerous possible ones undergone by the substrate. The apoenzyme decides the substrate specificity: it determines which substances react and which do not. The apoenzyme and coenzyme can in many cases be separated from each other by the various procedures; and often the reverse reaction can be carried out, which reproduces the enzyme. A coenzyme with various apoenzymes forms a series of enzymes capable of producing different effects.

The coenzyme is often identical with one of the vitamins or is structurally related to it, i.e., is a derivative of a vitamin. The vitamins constitute a group of substances which usually have a complex structure, often differ sharply from one another from the chemical standpoint and are classified together only by the biological function. They must be included, though in small amounts, in the diet; a deficiency of the vitamins causes a disease and their absence is even fatal to the organism. Consuming vitamins (and not only vitamins), human and animal organisms build up their enzymes.

A substance which serves as a vitamin for organisms of one species is not necessarily a vitamin for other organisms for two reasons: either these organisms do not use this particular enzyme or they can synthesize it themselves. For example, ascorbic acid is a vitamin for man, but it is not a vitamin for rats because the organism of rats produces it from glucose. Some vitamins are universal and are necessary for all organisms, from unicellular organisms (yeasts and bacteria) to man. Green plants are capable of producing all their substances from mineral compounds and carbon dioxide and, hence, do not need vitamins.

For a number of protein enzymes to function in the organism it is necessary that micro amounts of ions of some metals (Mg, Zn, Mo, Mn, Cu) be present in the organism. These metal ions are called **enzyme activators** and are not considered to be vitamins. Some coenzymes and the corresponding vitamins contain metals (iron, cobalt). Micro amounts of metals (*microelements*) play a very significant role in the growth of plants; probably, these microelements are used for building up enzymes and serve as "plant vitamins".

A special nomenclature of enzymes is based on the substrate principle. The substance upon which an enzyme acts is called its *substrate*. Enzymes are named by adding the suffix *-ase* to the root of the name of the substrate. Thus, for example, *protease* is the enzyme that hydrolyses protein, *amylase* acts on starch (amylum), *cellulase* on cellulose. Other enzymes have been given names indicating the type of reaction in which they are involved, such as *esterases*, and *transphosphorylase*. This nomenclature has widely been used in scientific literature and must be known to the reader, and therefore it is used in the following discussion. An international systematic nomenclature has been worked out, in which each enzyme is given a code consisting of four numbers which designate the class, subclass, subsubclass and the order of a particular enzyme in the sub-subclass. Six classes of enzymes and examples of subclasses and nomenclature codes in this system are given on page 461.

Enzymes as catalysts differ from ordinary catalysts. They are characterized by the following features:

1. Enzymes are much more specific with respect to the structure of the material being catalysed and to the reaction.
2. Enzymes exhibit complete stereochemical specificity.
3. Enzymatic reactions proceed at a much faster rate than the same reactions catalysed by conventional catalysts.
4. The temperature at which enzymes exhibit maximum activity is known as the **optimum temperature.** Enzymes function as catalysts at relatively low optimum temperatures (their activity falls sharply at 50°C and at temperatures of 50-80°C they fail to function).
5. Enzymes undergo denaturation, i.e., they irreversibly lose their catalytic activity when heated to 50-100°C. There exist, however, enzymes (trypsin, ribonuclease) whose activity is regained on cooling even after boiling.
6. For each enzyme there is a particular optimum acidity (pH value) of the medium at which its catalytic activity is at a maximum.

A confirmation for the first specificity will be given at a later time, in the discussion of proteolytic enzymes. The stereochemical specificity becomes clear from the fact that an enzyme active towards, say, an L-antipode will not act on the D-antipode, and vice versa. The third characteristic may be illustrated by the fact that for a definite amount of sucrose to be converted into invert sugar by hydrolysis per unit time there is required a hydrogen-ion concentration 10,000,000 times greater than the concentration of the enzyme invertase.

The high rate of enzymatic reactions is accounted for, on the one hand, by a considerable decrease in the activation energy of the reaction, as is always the case in catalysis. Thus, in the acid hydrolysis of casein the activation energy is 20.6 kcal/mole, while in the hydrolysis effected with the aid of trypsin only 12 kcal/mole is required. The hydrolysis of sucrose with acid requires an activation energy of 25.5 kcal/mole, while the enzymatic hydrolysis (with sucrase or invertase) only 12-13 kcal/mole is needed. On the other hand, the pre-exponential factor in the Arrhenius equation is no less important for enzymatic reactions since the value of this factor is, as a rule, greater by many orders of magnitude than in ordinary reactions. There is evidence that enzymes have an **active centre** (*cleft*), the part of the enzyme surface to which the substrate binds, and a second centre which effects the reaction. An enzyme may be active in the sense that it folds to bring its active centre closer to the site of its action, somewhat changing its secondary or tertiary structure.

25.1. Classification of Enzymes

Enzymes are usually classified according to the type of reaction which they catalyse:

1. **Oxidoreductases** which effect oxidation and reduction reactions, in particular, dehydrogenation reactions (*dehydrogenases*).
2. **Transferases** which bring about the transfer of various residues, such as acyl, phosphate, glycoside residues.
3. **Hydrolases** which effect hydrolysis.
4. **Lyases** which are responsible for the non-hydrolytic splitting of the C—C, C—O, C—S, and C—N bonds with the formation of double bonds and, in particular, for the occurrence of decarboxylation, and elimination of water, hydrogen sulphide, ammonia; they also effect addition reactions across double bonds.
5. **Isomerases** which effect intramolecular rearrangements; for example, **phosphoglucomutase** converts glucoso-1-phosphate into glucoso-6-phosphate.
6. **Ligases** or **synthetases** which catalyse the process of formation of new bonds: C—C, C—O, C—S, C—N; the reaction involves the cleavage of the pyrophosphate bond in adenosine triphosphate and it is this process that supplies energy for synthesis.

These six classes are divided into subclasses (the second number in the enzyme code according to the systematic nomenclature). The subclasses in their turn are divided into sub-subclasses (the third number in the code). Finally, there is a fourth number used to designate the order of a particular enzyme in the sub-subclass. Thus, for example, α-amylase which hydrolyses starch has the code 3.2.1.1, cellulase—3.2.1.4, aminopeptidase—3.4.1.2, pepsin—3.4.4.1, trypsin—3.4.4.4.

Among these classes of enzymes only hydrolases (class 3) have no prosthetic group and are pure proteins. It is therefore more convenient to begin the discussion of enzyme classes (which will be confined to some representatives) with hydrolases.

A. Hydrolases

The number of hydrolases is very great. As examples of individual groups of hydrolases may be cited esterases with subgroups of lipases (which hydrolyse fats), cholinesterases (which hydrolyse acetylcholine), phosphatases (which hydrolyse phosphate esters), glycosidases (which effect the hydrolysis of glycosidic linkages), amidases (which split the amide bond, say, of urea, with elimination of ammonia), proteases (which cleave peptide bonds), nucleases (which hydrolyse nucleic acids).

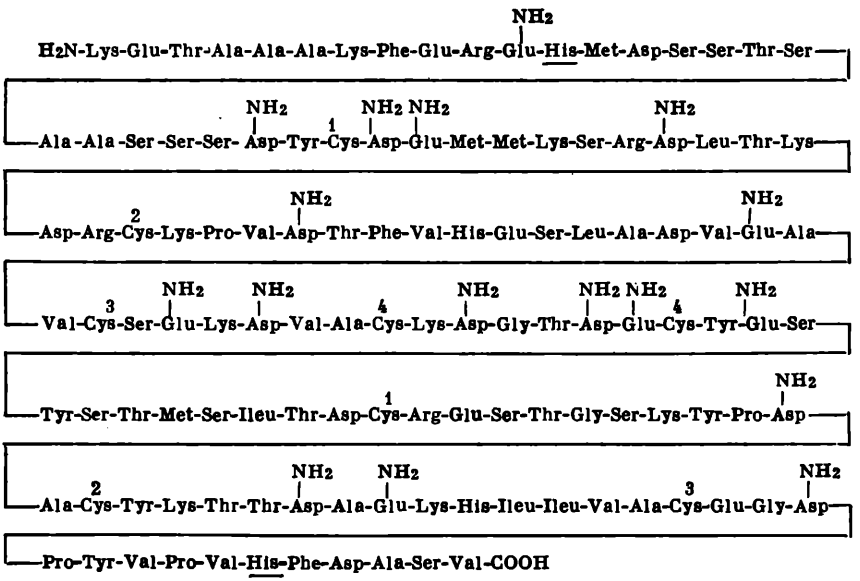
Here we shall briefly consider only the most thoroughly studied proteases which are subdivided into two large groups—exoproteases and endoproteases. **Exoproteases** hydrolyse the terminal amino acids of the protein or polypeptide chain and are, in their turn, subdivided into carboxypeptidases and aminopeptidases, depending on whether they split the end of the protein chain with the free carboxyl or amino group. **Endoproteases** split the protein molecule somewhere in the middle of the chain.

Proteases are widely distributed in the animal and plant kingdoms; there exist cellular proteases which effect the corresponding reactions inside the cells. Particularly known is papain which is isolated from the fruits of the papaw, *Carica papaya* (South America). But the most important and most thoroughly studied are the proteases that accelerate the breakdown of proteins in animals and human beings during the digestion of food. The stomach walls secrete the inactive protein (proenzyme) **pepsinogen**. Under the influence of the gastric juice and the pepsin present in it, the polypeptide chain is split off from pepsinogen which is converted into the active enzyme *pepsin*, which has a molecular weight of 35,000 and has long been obtained in the crystalline state. Pepsin at an optimum pH of 1.5-2.5 cleaves proteins predominantly at the site of both aromatic amino acids (tyrosine and phenylalanine) at their amino end. The amino acid next to the aromatic amino acid must have "hooks" for pepsin, such as the COOH or SH residues, and must have no free NH_2 group. These conditions, however, are sufficient for the hydrolysis of protein macromolecules to relatively short peptide chains in the stomach. The digestion of food in the duodenum and in the small intestines now takes place under alkaline conditions. The duodenum is supplied with enzymes by the pancreas which secretes the proenzymes—trypsinogen, chymotrypsinogen, and the proenzyme corresponding to carboxypeptidase. These proenzymes (like pepsinogen) are converted in the duodenum into the enzymes—trypsin, chymotrypsin and carboxypeptidase.

Chymotrypsin in alkaline medium (pH 8) hydrolyses in peptides predominantly the bonds of the same aromatic acids as does pepsin, but from the other side—the end with the carboxyl group. **Trypsin** disrupts peptide linkages from the side of the carboxyl group in lysine and arginine residues. **Carboxypeptidases** accomplish the hydrolysis of the terminal amino acid with the free carboxyl group. Such a hydrolysis but from the side of the amino-acid end of a protein or peptide is effected by **aminopeptidases.** These enzymes enter into the composition of the enzyme eliminations of the walls of small intestines. Here the digestion is completed by the full hydrolysis to amino acids as a result of the action of the enzyme **dipeptidase** on dipeptides. The amino acids are absorbed by the intestinal wall and enter the bloodstream.

We have already noted that each enzyme shows a high degree of specificity towards the structure of the portion of the protein molecule being hydrolysed, which is established experimentally by testing the hydrolytic action of the enzyme on the simplest peptides of known structure (di- and tripeptides). The stereochemical or configurational specificity of enzymes is also very pronounced: in particular, all the proteases mentioned above are active only with respect to peptides built up of L-amino acids. It is interesting that enzymes probably exhibit no specificity for the secondary and tertiary structures of the protein being hydrolysed, though the presence of these structures usually makes difficult the splitting of the protein by proteases. The enzymes themselves when being denatured, say, on heating up to 50-100°C, lose their activity, i.e., their activity is intimately associated with their own structure.

At present, intensive investigations are carried on with a view of elucidating the structure of digestive enzymes and, perhaps, it will be established in the nearest future. One should not, however, expect that the elucidation of the primary structure and even of the secondary and tertiary structures will immediately unravel the mystery of the catalytic action of enzymes. Thus, the structure of one of the phosphatases, **ribonuclease**, which hydrolyses the ribonucleic acids, has been established by Moore, Stein, and Anfinsen. The structure established is as follows:



In the long polypeptide chain of ribonuclease, the cysteine residues, marked by the same numerals, are linked in pairs by disulphide

bridges. Evidently, the amino-acid sequence in the ribonuclease molecule does not yet account in any way for its catalytic action on the linkage between phosphoric acid and ribose in RNA. Highly interesting are the investigations of ribonuclease carried out by Anfinsen. If β-hydroxyethylmercaptan acts on a solution of ribonuclease in aqueous ≈50 percent solution of urea (where the α-helix is completely destroyed) which cleaves all the S—S bridges, the enzymes will completely lose their catalytic activity. But if the resulting protein containing SH groups in place of S—S bridges and freed of the urea is oxidized with air, then all the SH groups will be oxidized in pairs to S—S bridges, the ribonuclease will regain its structure and, hence, its catalytic activity. Thus, the S—S bridges in the given protein (and this is typical) are reformed at the former sites and, undoubtedly, not only the secondary but also the tertiary structure characteristic of ribonuclease is recovered at the same time. But if the oxidation is conducted in a solution of urea where the ordinary hydrogen bonds of the secondary structure are broken, then the cross-linking will occur either randomly or in a different way and no active enzyme will obtain. Hence, as has been found in this particular case, not the disulphide bridges but the hydrogen bonds of the secondary structure predetermine the tertiary structure which brings definite cysteine SH groups closer together and makes possible their oxidation to cysteine S—S bridges. At the same time, it becomes clear that enzymatic activity is due to the primary, secondary and tertiary structure taken together.

For a number of enzymes, in particular, ribonuclease, it has however been demonstrated that not the molecule as a whole but only a part of it (its active site) is responsible for catalytic activity. Thus, using the enzyme subtilisin, Richards effected the splitting of the ribonuclease molecule across the linkage between the units 20 and 21 (the peptide bond of Ala—Ser) and in this case the molecule was preserved as an entity due to the secondary and tertiary structures. The enzymatic properties were also retained. But when subjected to chromatographic separation on an acid ion-exchanger a short peptide consisting of 20 amino-acid residues separated from the rest of the molecule. Both parts of the molecule were found to be devoid of enzymatic activity, but when they were mixed, the activity was restored. The separated, greater portion of the protein molecule was still capable of binding the enzymatic reaction substrate usual for ribonuclease but it could not cleave it. When ribonuclease is hydrolysed by carboxypeptidase and three amino acids—valine, serine, and alanine—are split off the C-terminal end, the activity of ribonuclease remains unaffected. The pepsin hydrolysis disrupts the fourth bond from the C-terminal end and splits off aspartic acid in addition to valine, serine and alanine. Then the ribonuclease residue completely loses its activity. In a similar way the signific-

ance of two His residues in positions 12 and 119 is established. What has been said above throws light on the investigation of the structure of protein as an enzyme.

In contrast to hydrolases, which are pure proteins (simple proteins), many, but not all, types of enzymes (conjugated protein enzymes which are also called **holoenzymes**) contain prosthetic groups (coenzymes), which have been extensively studied, while the structure of the apoenzyme is still unknown.

B. Transferases

The enzymes of class 2, which are also called **group-transferring enzymes**, fall into the following subclasses:

2.1. Enzymes transferring C_1-groups (methyltransferases, hydroxymethyl- and formyltransferases, etc.).

2.2. Enzymes transferring aldehyde and keto groups.

2.3. Enzymes transferring acyl groups (acyltransferases).

2.4. Enzymes transferring glycosyl residues (glycosyltransferases).

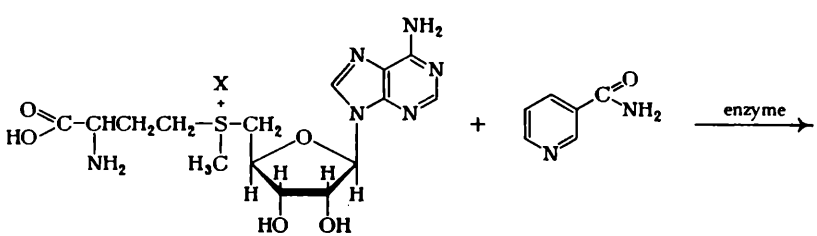
2.5. Enzymes transferring alkyls (alkyltransferases).

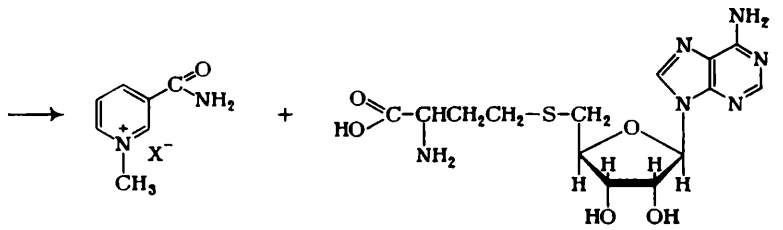
2.6. Enzymes transferring N-containing groups (aminotransferases, amidinotransferases, and hydroxyaminotransferases).

2.7. Enzymes transferring phosphate residues (phosphatetransferases).

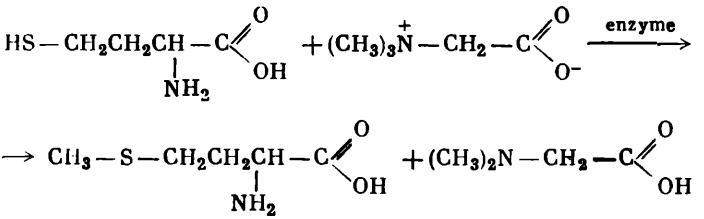
2.8. Enzymes transferring sulphur-containing groups (including those transferring coenzyme A).

Let us first consider methyltransferases (code 2.1.1), which transfer methyl (in particular, the methyl group of the methionine molecule is transferred). An example is **nicotinamide-methyltransferase** which catalyses the methylation of nicotinamide at the heterocyclic nitrogen atom, transferring the methyl group from methionine bound into S-adenosylmethionine. The latter is thus converted into S-adenosylhomocysteine:





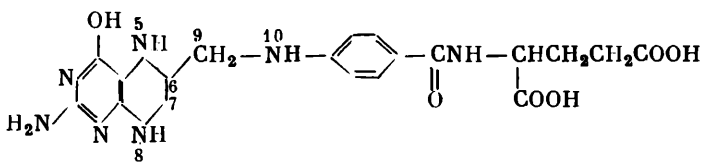
The resulting homocysteine is again methylated, in particular, due to the methyl of betaine, by means of the enzyme **betaine-α-homocysteine-methyltransferase**:



Methyltransferases (transmethylases) are regarded at present as single-component protein-enzymes which act on two substrates: on the donor (adenosylmethionine, "active methyl") and on any acceptor of the methyl group. If the methylated acceptor has an onium structure (betaines), then the transmethylation reaction is reversible. Thus, adenosylmethionine serves not as a coenzyme but as a metabolite-transferring agent which might better be called a **cosubstrate.**

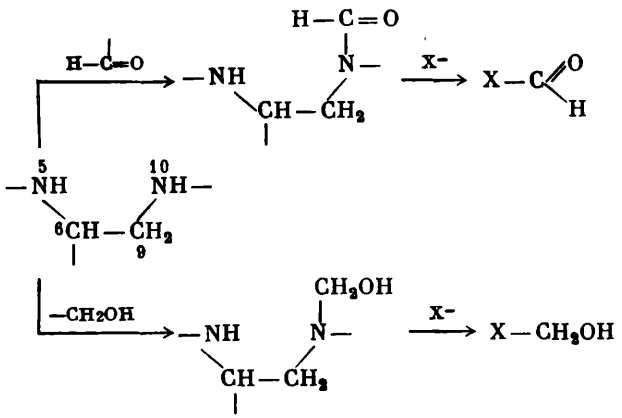
In certain cases (e.g., in the biosynthesis of methionine and thymidine) the role of coenzymes transferring CH_3 groups is played by the coenzyme forms of vitamin B_{12} or by tetrahydrofolic acids.

The enzymes of subclass 2.1.2 transfer the one-carbon residues $-CH_2OH$ and $-CHO$ (but not $-COOH$) and contain, as a coenzyme, 5,6,7,8-tetrahydrofolic (pteroylglutamic or folic) acid



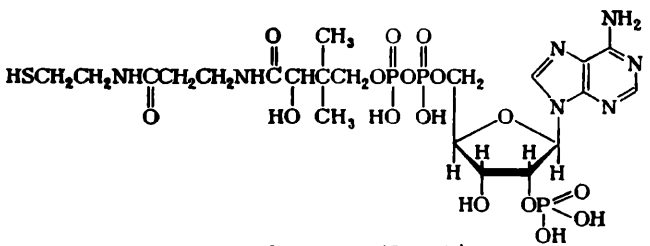
It is the grouping of atoms 5, 6, 9, and 10 of this acid that serves as a reaction centre for the transfer of hydroxymethyl and formyl groups according to the scheme in which the anion X^- acts as an

acceptor of these groups:



Enzymes of this kind play a part in the synthesis of purine bases and certain amino acids.

The transferases of subclass 2.3 that deserve mention here are **acyltransferases.** Their coenzyme is called coenzyme A (the "A" standing for acylation) often abbreviated to CoA or CoA—SH. It contains the structural units of pantothenic acid and 3'-phosphoadenosine-5'-pyrophosphate and has the following structure:



Coenzyme A (CoA-SH)

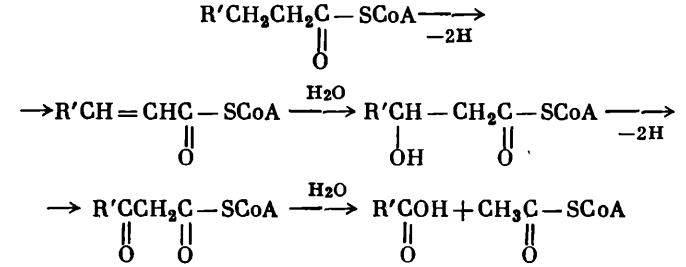
The transfer of the acyl group by means of CoA — SH is formulated by the following scheme:

$$RCO^- + ATP + CoA-SH \longrightarrow RC(=O)-SCoA + ADP + H_2PO_4^-$$

(ATP=adenosine triphosphate; ADP=adenosine diphosphate)

The role of adenosine triphosphate is to supply energy for effecting the process. The grouping RCO—SCoA transfers the acyl group to the substrate. It is this mechanism which underlies the biogenic transformation of acetic acid into isoprenoids via acetoacetic acid and mevalonic acid (page 328). The oxidation of fatty acids in the

organism also proceeds through the stage of formation of RCO—SCoA. After this group has been formed there takes place dehydrogenation under the influence of a dehydrogenating enzyme and a double bond is formed in the radical R at the α,β-positions (this is, of course, outside the scope of transferases). There then occurs hydration followed by the dehydrogenation of the β-hydroxy compound to a derivative of the β-keto acid and, finally, the elimination of the CH_3CO—SCoA takes place with the formation of a fatty acid containing two carbon atoms less than the parent acid:

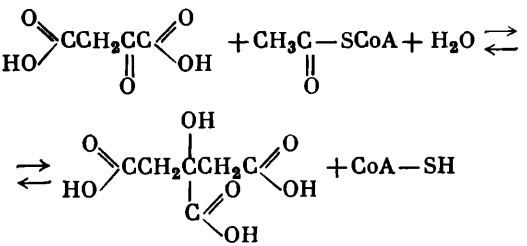


Then the process is repeated.

The synthesis of fatty acids in the body takes a reverse route.

Coenzyme A effects the numerous reactions of acetylation of alcohols, hydroxy acids, amines, cysteine, etc., and also acylates carboxylic acids at the second carbon atom, forming β-keto acids (in the Krebs cycle, see Volume II, page 135).

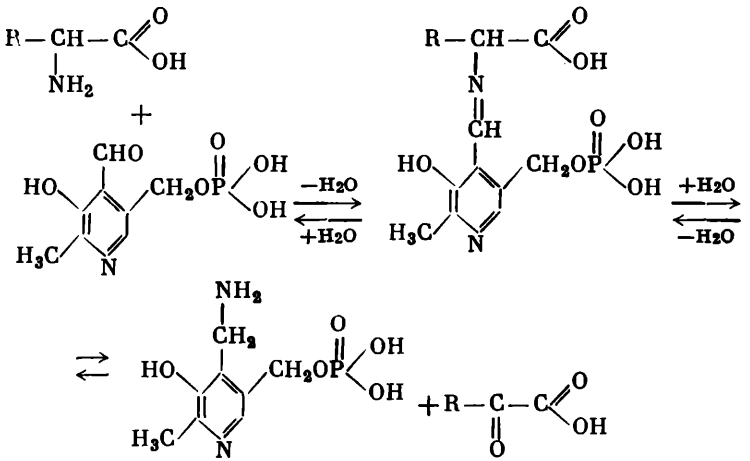
Moreover, coenzyme A enters into condensation (via its α-carbon atom) with oxalacetic acid, forming citric acid (which is also one of the stages of the Krebs cycle)



Of the transferases of subclass 2.7 mention should be made of **phosphatetransferases** which effect the transfer of the phosphoric acid residue from adenosine triphosphate (see Volume II, page 131) to the substrate, for example, to glucose (**glucokinase**) and fructose (fructokinase), in the fermentation process.

Transferases also include **aminotransferases**, or *transaminases* (A. E. Braunshtein), such as **glutamate transaminase** and **alanine transaminase**, which exchange the functional groups in the corre-

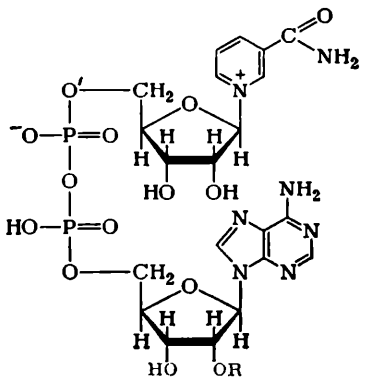
sponding α-amino acids and α-keto acids. The coenzyme of aminotransferases is **pyridoxal-5-phosphate** and, hence, it is transferases that are formed with the participation of vitamin B_6. The coenzyme of transaminases functions according to the following scheme:



As a rule, in living cells the commonest amino-group donor is glutamic acid: the most intensive is the reversible transfer of amino groups between glutamic acid and oxalacetic acid (for more detail, see Volume III, page 395).

C. Oxidoreductases

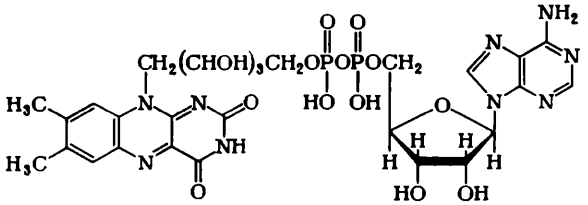
This group of enzymes of biological oxidation and reduction (class 1) is very large. All oxidoreductases have coenzymes. The commonest of them are two nicotinamide coenzymes: **nicotinamide-adenine dinucleotide** (NAD) and **nicotinamide-adenine dinucleotide phosphate** (NADP), which contain, as a hydrogen acceptor, the amide of nicotinic acid, nicotinamide or niacinamide (vitamin PP), alkylated at the heterocyclic nitrogen:



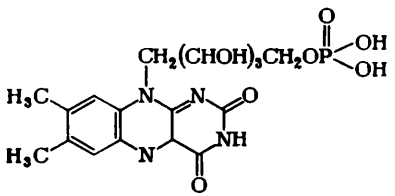
R=H..... NAD (or Codehydrogenase I)

R=PO_3H_2.... NADP (or Codehydrogenase II)

There are also flavin coenzymes: **flavin-adenine dinucleotide** (FAD) and **flavin mononucleotide** (FMN), in which riboflavin (vitamin B_2) serves as a hydrogen acceptor:

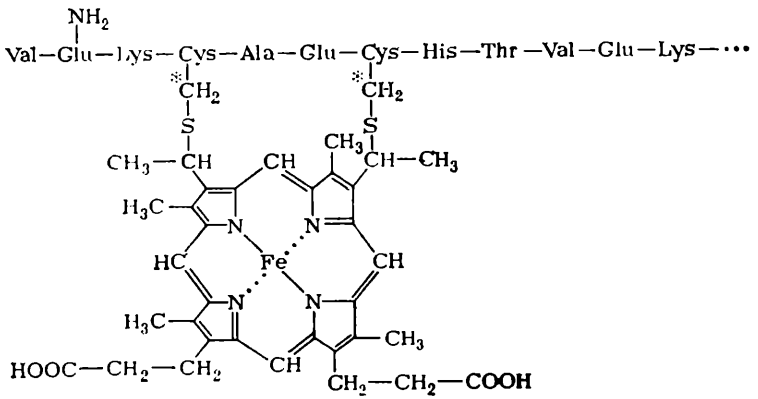


FAD



FMN

The coenzymes of a large group of oxidoreductases are **heme** (Volume III, page 349) and structurally related iron porphyrins; oxidoreductases with such coenzymes are called **cytochromes.** In cytochromes, the heme is linked to protein via the sulphur atoms of cysteine:

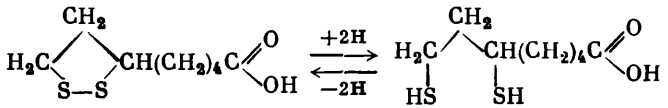


(in the sites marked with asterisks the grouping —S—CH_2— is picked, for clarity, out of the symbol Cys, i.e., the abbreviation

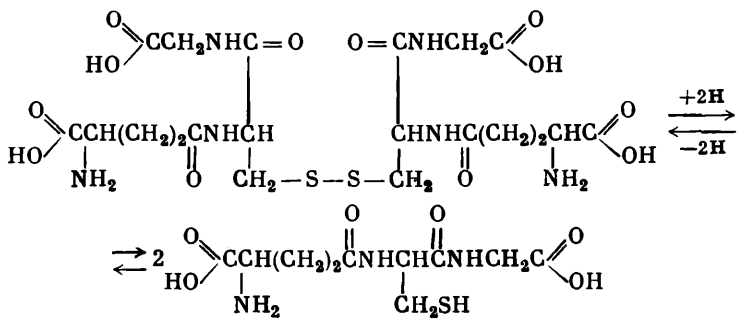
Cys that usually designates the cysteine residue —NH—CH—CO—, here represents only the grouping —NH—CH—CO—).

The redox effect of cytochromes is based on the reversible change of the valency of the central iron atom between the divalent (Fe^{2+}) and the trivalent (Fe^{3+}) state.

Apart from the cytochromes, there are many other iron-containing oxidoreductases (catalases, peroxidases, ferrodoxins, hydroxylases), and also copper-containing oxidoreductases (phenolases, ceruloplasmins, aminooxidases, etc.). Finally, in a number of oxidation-reduction processes the role of the hydrogen acceptor is performed by lipoic (or thioctic) acid, glutathione, and the derivatives of *p*-benzoquinone and 1,4-naphthoquinone—ubiquinones and tocopherol quinones.



Lipoic acid



Glutathione

The oxidation in cells occurs in a complicated way. The hydrogen atoms are transferred to the oxygen molecule via a number of stages by means of a series of enzymes. This multistage process may be formulated by the following scheme:

I. $\underset{\text{(dehydrogenase)}}{\text{NAD-H}_2\text{—enzyme}} + \underset{\text{enzyme}}{\text{Flavin}} \xrightarrow{H^+} \text{NAD-enzyme} + \underset{\text{enzyme}}{\text{H}_2\text{-Flavin}}$

II. $2\ \text{Cytochrome}\ (Fe^{2+}) + \frac{1}{2}\,O_2 \longrightarrow 2\ \text{Cytochrome}\ (Fe^{3+}) + O^{2-}$

III. $O^{2-} + 2H^+ \longrightarrow H_2O$

IV. $2\ \text{Cytochrome}\ (Fe^{3+}) - \underset{\text{enzyme}}{H_2\text{-Flavin}} \longrightarrow 2\ \text{Cytochrome}\ (Fe^{2+}) + \underset{\text{enzyme}}{\text{Flavin}} + 2H^+$

Oxidoreductases (class 1) are divided into subclasses (the second numeral) according to the group being oxidized, i.e., the group that gives its hydrogen or electrons:

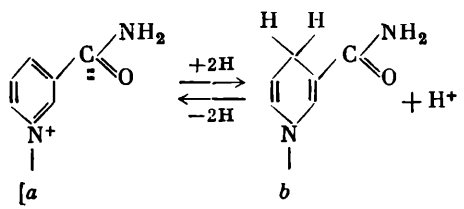
1.1. CHOH.
1.2. Aldehydes and ketones.
1.3. $\rangle CH-CH\langle$.
1.4. $\rangle CH-NH_2$.
1.5. $\rangle C=NH$.
1.6. NAD$\langle^{H}_{H}$ or NADP$\langle^{H}_{H}$.
1.7. Other nitrogen-containing compounds.
1.8. Sulphur compounds.
1.9. Heme.
1.10. Bis-Phenols.
1.11. Hydrogen peroxide as acceptor.
1.12. The hydrogen molecule (H_2).

The division of this subclass into sub-subclasses is based on the hydrogen or electron-acceptor principle. For example, subclass 1.1 (hydrogen donor) is divided into the following sub-subclasses:

1.1.1. With NAD or NADP as acceptor.
1.1.2. With a cytochrome as acceptor.
1.1.3. With O_2 as acceptor.

The total number of oxidoreductases known at present with the coenzymes given above is about 250. We shall confine ourselves only to some representative examples to illustrate the principle of their action.

Let us first consider the coenzymes NAD and NADP (which were formerly known as codehydrogenases I and II). These coenzymes break down on hydrolysis into nicotinamide (niacinamide), ribose, phosphoric acid, and adenine-N-riboside. The redox function is performed here by the nicotinamide residue:

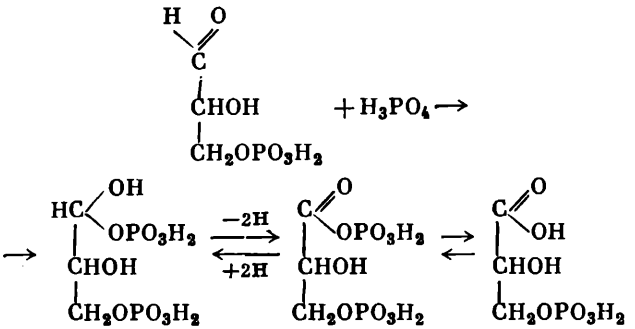


The form *a* dehydrogenates the substrate and the form *b* hydrogenates it. The structure and synthesis of nicotinamide (vitamin PP)

has already been discussed (see Volume III, page 393). The codehydrogenases play a part in many biological reactions (in carbohydrate, fat, and protein metabolism).

We shall cite only the most typical reactions catalysed by enzymes with coenzymes NAD and NADP.

1. The dehydrogenation of glyceraldehyde phosphate to diphosphoglycerate in the fermentation of sugars:

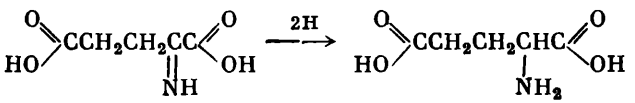


2. The dehydrogenation of saturated fatty acids to form the corresponding unsaturated acids (with participation of NADP).

3. The hydrogenation of acetaldehyde to give ethanol in alcoholic fermentation.

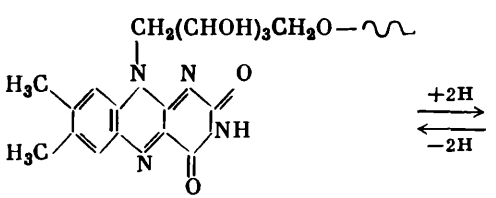
4. The hydrogenation of pyruvic acid to yield lactic acid in muscles and in lactic acid fermentation.

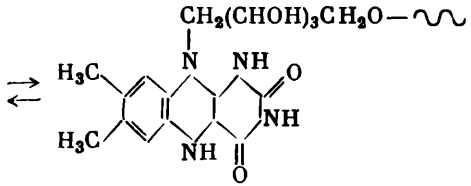
5. The hydrogenation of iminoglutaric acid to give L-glutamic acid as a stage in the reductive amination of α-ketoglutaric acid:



Each of these reactions requires a specific enzyme.

The coenzymes of many aerobic and some anaerobic oxidoreductases are **flavin-adenine dinucleotide** (FAD) and, less often, **flavin mononucleotide** (FMN), the basic structural unit of which is the riboflavin molecule (vitamin B_2). Accepting and donating hydrogen, the vitamin part of these coenzymes (the complete structure is given on page 470 *et seq.*) changes its structure in the following manner:





Vitamin B_2 (riboflavin) is a component of the famous oxidation Warburg yellow enzyme (1932) which was isolated from yeast. It was also isolated from milk, eggs, and from the microorganisms of the species *Eremothecium ashbyi*, which contain up to 2 per cent of riboflavin, and are used for its production.

D. Lyases

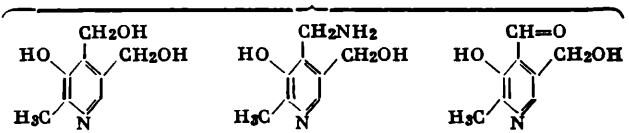
The lyases (class 4) include enzymes cleaving C—C bonds (subclass 4.1). Mention should first be made of numerous **decarboxylases**, which split off the carboxyl group from carboxylic acids, in particular, from hydroxy acids, aldehydic and ketonic acids, amino acids; **aldehyde-lyases**, which split off, say, glyceraldehyde from fructoso-1-phosphate, the glyceraldehyde being then transformed into dioxyacetone (the enzyme aldolase). Aldehyde-lyases also convert the amino acid threonine into glycine + acetaldehyde, eliminate benzaldehyde from its hydroxynitrile, etc.

The lyases of subclass 4.2 bring about the cleavage of C—O bonds. Examples are a number of **dehydratases**, which dehydrate, for example, malic acid to give fumaric acid. Subclass 4.3 include C—N lyases, which mainly split ammonia from amino acids. Subclass 4.4 includes C—S lyases. There are also C—Hal lyases (subclass 4.5). The only enzyme of this subclass known so far is the DDT-hydrochloride-lyase of insects.

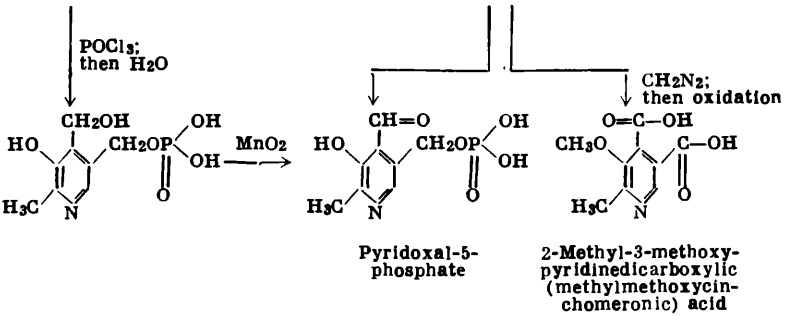
Of the coenzymes of lyases mention should first be made of the **codecarboxylase—pyridoxal-5-phosphate**, which has, as its basic structural unit, the pyridoxal molecule (one of the vitamins of the B_6 group). As has already been noted (see Volume III, page 395), pyridoxal-5-phosphate is also the coenzyme of transaminases which play a very important part in protein metabolism (the reaction of transamination of α-keto acids and α-amino acids).

The relation between group B_6 vitamins and pyridoxal-5-phosphate, which are interconvertible in the organism, can be deduced from the following formulas:

Group B_6 vitamins



Pyridoxin (adermin) Pyridoxamine Pyridoxal



Indeed, when pyridoxin is acted on by phosphorus oxychloride, its 5-hydroxymethyl group is esterified with the least steric hindrances, and after treatment with water there is formed pyridoxin-5-phosphate, which is then oxidized to the aldehyde pyridoxal-5-phosphate.

The structure of codecarboxylase (like that of pyridoxal itself) follows from functional analysis which shows the presence of one aldehyde group, one primary alcoholic group (or its phosphoric ester), one phenolic hydroxyl group and one methyl group, and also from its oxidation after methylation with diazomethane to 2-methyl-3-methoxypyridinecarboxylic acid (methylmethoxycinchomeronic acid). For the synthesis of group B_6 vitamins, see Volume III, page 393.

Combining with various apoenzymes, whose structures are largely unknown, pyridoxal phosphate forms a variety of decarboxylases, in particular, amino-acids decarboxylases capable of converting amino acids into the corresponding amines; the decarboxylation of each amino acid requires a specific decarboxylase. With other apoenzymes pyridoxal phosphate affords transaminases which are also specific for each of the amino acids.

The lyases include the pyruvic-acid decarboxylase which was formerly termed α-carboxylase. Its coenzyme is thiamine pyrophosphate (the characteristic component is thiamine, vitamin B_1) which was isolated by the founder of the theory of vitamins, Funk, in 1912 from the powdery rice polishings (their extract is used in the treatment of the disease "beri-beri" (polyneuritis) which is widespread among those living on polished rice. The structure of vitamin B_1 has already been discussed (Volume III, page 411).

The decarboxylase, whose coenzyme is thiamine pyrophosphate, catalyses the splitting-off of carbon dioxide from pyruvic acid in the degradation of glucose in alcoholic fermentation and on cellular respiration. When deficiency occurs, pyruvic acid accumulates in the organism instead of undergoing further degradation, with results that may lead to polyneuritis.

E. Isomerases

Isomerases constitute class 5 of enzymes, which is divided into the following subclasses:

5.1. Racemases and epimerases which cause the stereoisomerization. The racemases of amino acids often contain pyridoxal phosphate as coenzyme.

5.2. *Cis-trans* isomerases (maleylacetoacetate isomerase).

5.3. Intramolecular oxidoreductases which effect, for example, the interconversions of aldoses and ketoses.

5.4. Intramolecular transferases which transfer intramolecularly acyl and phosphoryl (phosphate) residues, and the methyl group. The coenzymes of some of them is vitamin B_{12} (see Volume III, page 351).

5.5. Intramolecular lyases.

F. Synthetases

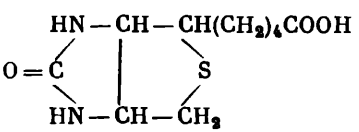
Synthetases (ligases) are enzymes that join together two molecules. They are divided into enzymes forming the following bonds: C—O (subclass 6.1); C—S bonds (subclass 6.2); C—N bonds (subclass 6.3); and, finally, C—C bonds (subclass 6.4).

The most common type of reactions of ligases forming C—O bonds is the binding of amino acids with ribonucleic acids (amino-acid-RNA ligases) with the participation of adenosine triphosphate (ATP), which supplies energy and is converted into adenosine diphosphate (ADP).

Lyases forming C—N bonds bring about the acetylation of coenzyme A (page 467) due to the acetate ion through the mediation of ATP as a source of energy, and also analogous acylation reactions.

The characteristic lyases of subclass 3 are amide-synthetases (for example, they convert aspartic acid into its amide—asparagine) and peptide-synthetases (e.g., ligases which synthesize glutathione).

Lastly, C—C ligases (subclass 6.4) include carboxylases, in which the prosthetic group is β-biotin (Volume III, page 368). They accomplish the introduction of a carboxyl group into pyruvic acid through the action of carbon dioxide through the mediation of ATP (oxalacetic acid is formed), the introduction of a carboxyl group into acetyl-CoA (malonyl-CoA is formed), etc. The first reaction is of the utmost importance in the Krebs cycle (Volume II, page 135). In biotinyl enzymes, β-biotin



is covalently linked via the amide bond to the ε-NH_2 group of the lysine residue of the apoenzyme. During the action of these enzymes a molecule of carbon dioxide adds on to the ureidic group of biotin with the formation of a complex, N-carboxybiotinyl enzyme (the "active" form of carbonic acid). The reaction of formation of the complex is associated with the dephosphorylation of ATP to ADP.

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Academician ALEKSANDR NIKOLAEVICH NESMEYANOV was one of the most distinguished organic chemists of our time. He conducted fundamental research in the field of organoelement chemistry and authored important and original works on organic and theoretical chemistry. The concept of organoelement (elemento-organic) chemistry was introduced by A.N. Nesmeyanov. He devised diazo method of synthesis of organometallic compounds, discovered new classes of compounds, demonstrated relationship between structure and reactivity of metallic derivatives of tautomeric systems. His principal areas of interest were the chemistry of organometallic compounds and general problems of organic chemistry. Nesmeyanov initiated and directed a number of new trends of investigation, one of which was the preparation of synthetic and artificial food. Among the practical achievements in the investigations carried out by Nesmeyanov and his school may be mentioned the development of valuable medicinal preparations, the synthesis of a new antiknock compound and the preparation of a number of materials for special technical applications.
Nesmeyanov was awarded the State Prize for his investigations in the field of organoelement compounds and the Lenin Prize for his remarkable contributions to the development of the science and practical implementation of the scientific achievements in the national economy.
A. Nesmeyanov was an honorary member of the Royal Society (Great Britain), and of academies of science of many countries, including the New York Academy of Sciences (USA).
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